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## FURTHER OBSERVATIONS ON PARAMOEBA HOMINIS. AN INTESTINAL PARASITE OF MAN\*

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WASHINGTON, D. C.

In August, 1906, in a preliminary communication, published in the *American Journal of the Medical Sciences*, I described a new intestinal parasite of man, which, because of its life-history, I included in the genus *Paramoeba*, established by Schaudinn, naming the organism *Paramoeba hominis*. The object of the present paper is to record further observations on this interesting parasite and to call attention to its probable occurrence in patients suffering from chronic diarrhea, in which the attacks alternate with periods of constipation, thus resembling quite closely the clinical picture of the form of dysentery due to the invasion of the intestine by *Entamoeba histolytica*.

### FREQUENCY OF OCCURRENCE OF PARAMOEBA HOMINIS

This species of amoeba was first observed in the feces of a Filipino suffering from an attack of chronic diarrhea, and I afterward found the same organism in the feces of five other Filipinos. At the time that I published my original description, I had never observed the parasite in the feces of American soldiers or civilians, or in Europeans, although I looked very carefully for it, and many of the Americans examined had resided in the Philippines for considerable periods of time. Since returning from the Philippines, and while in charge of the army laboratory at Fort Leavenworth, Kansas, I was so fortunate as to be able to study this parasite in three American soldiers, all of whom had just returned from the Philippine Islands, and all of whom entered the hospital because of recurrent attacks of diarrhea.

Their infection, in all probability, was contracted in the Philippines, and it may well be that infection with this parasite is much more frequent than is believed, having been confused with infection with *Entamoeba histolytica*, *Entamoeba coli*, or *Trichomonas hominis*. I am of the opinion, moreover, that careful research will result in proving that this parasite also occurs in this country, for chronic forms of diarrhea are of common occurrence in many portions of the United States, and monads are fre-

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\* This report by Dr. Craig, Captain, Medical Corps, U. S. Army, is from the Laboratory of the Surgeon-General's Office, Washington, D. C.

quently reported as occurring in the feces. The confusion of the flagellate stage of *Paramoeba hominis* with monads is very liable to occur unless one is well acquainted with the protozoa found in the human intestine and I believe that it is not at all unlikely that many of the cases of so-called monadic diarrhea, or dysentery, are in reality infections with *Paramoeba hominis*. It must be admitted, however, that infection with this parasite is rare as compared with the other species of amebas infesting man, or with infections with *Trichomonas hominis*, *Lambliæ intestinalis* (*Cercomonas intestinalis*), or even *Balantidium coli*, for in my own experience, covering the microscopic examination of several hundred specimens of feces from as many individuals, both in health and in disease, I have found this organism in only nine patients, three of whom were American soldiers, and six native Filipinos.

#### CLASSIFICATION

In 1896, Schaudinn<sup>1</sup> described an ameba occurring in sea-water, in which a flagellate stage of development alternated with an amebic stage. This ameba, after multiplying for several generations by simple division, at the end of its vegetative life becomes encysted, and within the cyst changes occur which eventuate in the formation of swarm-spores, which are liberated, and after living as flagellates, and multiplying by longitudinal division, at length lose their flagella, and again become typical amebas. The process of spore formation, as described by Schaudinn, consists in the fragmentation of the nucleus of the encysted ameba, preceded by the division of a cytoplasmic body in contact with the nucleus, called the *Nebenkörper*, which acts as a centrosome or blepharoplast. The number of swarm-spores corresponds to the number of the divisions of the *Nebenkörper*, each swarm-spore consisting of a portion of the original nucleus and of the cytoplasmic body.

After the formation of the swarm-spores is complete they become flagellated, escape from the cyst in which they have developed, and after swimming about actively for an indefinite time, undergo longitudinal division and finally, losing their flagella, develop into typical amebas, which multiply by simple division, and again repeat the process of encystment and spore formation.

Schaudinn placed this organism in a new genus, *Paramoeba*, giving it the specific name, *eilhardi*, and, until my description of *Paramoeba hominis*, the genus was not known to contain organisms living within man.

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1. Schaudinn: Ueber den Zeugungskreis von *Paramoeba eilhardi*, neues Genus, neue Species, Sitzungsber. d. k. preuss. Akad. d. Wissensch., Berlin, 1896, pp. 31-41.

The ameba I described in 1906, like *Paramoeba eilhardi*, passes through both an amebic and flagellate stage during its life-cycle, and for this reason, and because the structure of the organism was very similar to *Paramoeba eilhardi*, I did not hesitate to place it in Schaudinn's genus, *Paramoeba*. Doflein<sup>2</sup> thinks that further research will show that the parasite I described should be placed in a new genus, but certainly all of the evidence that I have been able to adduce indicates that it belongs to the genus, *Paramoeba*, and while more extended knowledge of the parasite may result in its being placed in a new genus, I believe that at this time it should be regarded as belonging to the genus *Paramoeba*.

At the time of my original description I had not been able to demonstrate the occurrence of longitudinal division in the flagellate stage but I have since observed certain phenomena which are convincing as to the occurrence of this form of multiplication in the flagellate organisms, and which have enabled me completely to confirm Schaudinn's description of the life-cycle of *Paramoeba eilhardi*, so far as it relates to *Paramoeba hominis*, and therefore I am convinced that this parasite is properly placed in the genus *Paramoeba*, and that this genus must now be regarded as containing a species capable of existing as a parasite in man.

#### THE LIFE-CYCLE OF PARAMOEBA HOMINIS

As has been mentioned, this parasite has a complicated life-cycle, passing through both an amebic and a flagellate stage of existence. By making repeated examinations of the feces from patients infected with this parasite I have been able to trace the life-cycle of the organism during every stage of its development, and while I have been unable to reach definite conclusions regarding certain points connected with this development, such as the conditions hastening or retarding the various stages of growth, or the intervals of time which elapse between the amebic and flagellate stage, and the time consumed in the development of the swarm-spores, I have been able to study each stage of development and to observe the process of encystment; the formation of the swarm-spores; the process of longitudinal division of the flagellate forms; and the development of the amebic stage from the flagellate stage. The life-cycle of this parasite may be understood by consulting the diagram (Fig. 1) which accompanies this paper, and may be briefly described as follows:

Beginning with the amebic stage, the parasite reproduces by simple division for a certain period (probably as long as conditions are favorable to its vegetative existence), during which time its structure is that of a

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2. Doflein: Lehrbuch der Protozoenkunde, Berlin, 1909, p. 512.

typical ameba possessing blunt pseudopodia, and moving about as is usual with this class of organisms. Encystment is initiated by the organism becoming motionless, assuming a perfectly spherical form, and then rotating rapidly, the cyst wall being formed during the process of rotation. When encystment is complete, the organism again becomes motionless, and the refractive, double-outlined cyst-wall is then distinguishable. Within the cyst there soon appear numerous small, round, refractile bodies, which finally escape from the cyst; each body possesses a single, long flagellum, very delicate in structure. These little flagellates are actively motile, increase considerably in size, and undergo longitudinal division for several generations. At the end of this period of reproduction the parasites become motionless; the flagellum disappears; the border

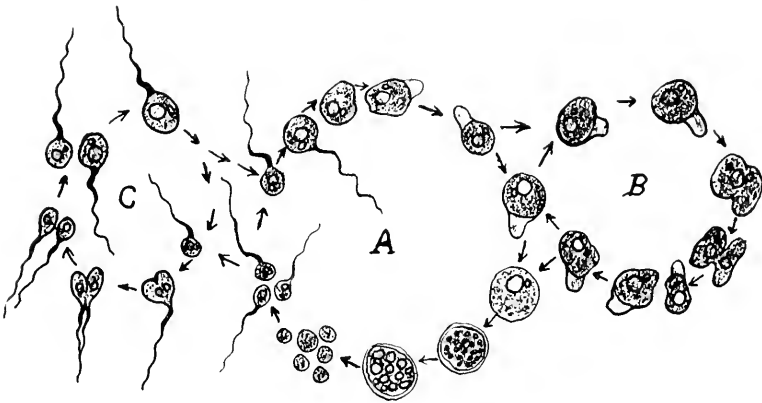


Fig. 1.—Diagram of the life-cycle of *Paramoeba hominis*. A, the entire life-cycle, showing the ameba and the flagellate stages, as well as the stage of encystment. B, reproduction of the amebic stage by simple division, or cycle of reproduction by simple division. C, reproduction of the flagellate stage by longitudinal division, or cycle of reproduction by longitudinal division.

of the spherical body remaining may be observed to undulate; and eventually a blunt, well-defined pseudopodium appears, and the parasite enters on its amebic stage of existence.

The occurrence of a species of ameba, possessing, as this species does, a flagellate stage of development, is of great importance and interest from a biological standpoint, in view of the occurrence of flagellate stages in such organisms as the *Leishmania*, and would appear to indicate that these organisms are more closely related than is generally believed and that such flagellate stages of development occur even in the *Rhizopoda*. It is logical, moreover, to believe that in *Paramoeba cilhardi* and *Paramoeba*

*hominis* we have organisms which occupy a position between the *Rhizopoda* and the *Flagellata*, serving, one may say, as a connecting link between these two great classes of the protozoa.

#### THE MORPHOLOGY OF *PARAMOEBA HOMINIS*

The morphology of *Paramoeba hominis* varies greatly in its different stages of development and for this reason it is necessary to describe the morphology presented in each stage, i. e., the amebic stage, the encysted stage, and the flagellate stage.

##### 1. *The Amebic Stage*

The organisms during this stage of development measure from 10 to 25 microns in diameter, the average measurement being about 18 to 20 microns. In those amebas which have originated from the flagellate stage, ameboid motion is first apparent as an undulatory movement of the periphery of the parasite, followed by the projection of small, bluntly conical pseudopodia. In those amebas which result from simple division, ameboid motility is first manifest in the projection of pseudopodia. In the youngest organisms ameboid motility is very sluggish, progressive motion being absent in many instances, although the pseudopodia may be projected and withdrawn with great rapidity; in the larger and older amebas progressive motion is well marked, and quite rapid, the ectoplasmic pseudopodia being projected and the endoplasm flowing into them immediately.

When these amebas are motionless, the ectoplasm and endoplasm cannot be differentiated, but when they are moving, even in the smallest amebas, these two divisions of the protoplasm may be easily distinguished, the endoplasm being more refractive and apparently of greater consistence than the ectoplasm, which is thin and veil-like in appearance. The endoplasm composes at least three-fourths of the substance of the parasite, and is finely granular in structure; the ectoplasm appears homogeneous in structure and of very slight consistence. The endoplasm may contain bacteria, crystals, diatoms, and occasionally, one or more red blood corpuscles. The greater degree of refraction of the endoplasm of *Paramoeba hominis*, as compared with the ectoplasm, serves to distinguish the amebic stage of this organism from *Entamoeba histolytica*, and *Entamoeba tetragena*, in which the ectoplasm is more refractive than the endoplasm; and from *Entamoeba coli*, in which there is practically no distinction between the ectoplasm and endoplasm.

A nucleus can be easily distinguished in even the smallest amebas, appearing as a refractive, spherical body surrounded by a rather thick, very refractive, granular nuclear membrane, which, in the larger organ-

isms, often appears to be composed of brightly refractive rods arranged, end to end, around the periphery of the less refractive nuclear substance. In the fully developed amebas (the larger forms) an oval body may be observed, lying in contact with, or very near the nucleus, and about one-third the size of the latter. This body undoubtedly corresponds to the cytoplasmic body (*Nebenkörper*, centrosome, or blepharoplast) described by Schaudinn in *Paramoeba cilhardi*.

A nutritive vacuole is not present in this ameba so far as I have been able to determine, although some of the organisms contain oval bodies suggestive of minute vacuoles.

When reproducing by simple division, the cytoplasmic body appears to divide first, quickly followed by the nucleus, and finally by the protoplasm, two daughter amebas being thus produced.

The organism in the amebic stage stains but poorly, although it may be stained with Wright's stain, Heidenhain's iron hematoxylin, carbol-fuchsin, Borrel blue, and methylene blue. The ectoplasm and endoplasm are not differentiated by any of these stains, but the nucleus stains fairly well, and when the organism is dividing may show well-marked mitotic figures. With Wright's stain, the nucleus appears to be composed almost entirely of chromatin, staining a pink, or reddish violet, while the cytoplasmic body, or *Nebenkörper*, may sometimes be distinguished as a deep violet or almost black body, lying in contact with the nucleus.

## 2. The Encysted Stage

The organisms which are about to encyst appear somewhat smaller than the average ameba, measuring from 15 to 20 microns in diameter, and are more granular in structure. Ameboid motility is absent and the ectoplasm and endoplasm are indistinguishable. Reproduction of the amebic stage is frequently observed, but in the same specimen of feces the precystic bodies just mentioned may be seen, as well as those in which the process of encystment is complete.

If one of these precystic amebas be watched it will be observed that it suddenly begins to rotate quite rapidly, and that this rotation may last for an hour, or even longer, although generally it ceases within fifteen minutes. During this process of rotation the cyst wall is formed, for when it ceases it will be observed that the organism is surrounded by a well-defined double-outlined, refractive capsule, which sometimes appears slightly mammillated. During rotation the organism contracts somewhat, most of the cysts measuring from 15 to 18 microns in diameter.

In the earliest stage of encystment the nucleus can be still distinguished, situated a little to one side of the center of the cyst, spherical

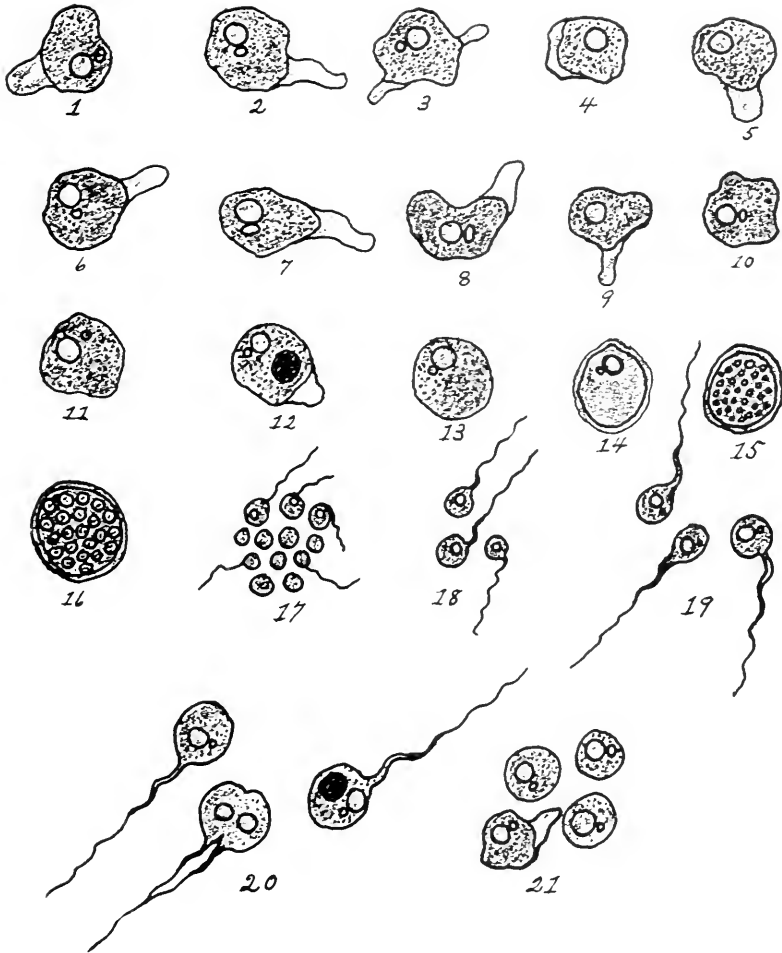


Fig. 2.—Various forms of the amebic, cystic, and flagellate stages of the *Paramoeba hominis*; (1 to 13) various forms of the amebic stage of *Paramoeba hominis* (note the well-defined nucleus, the oval or round cytoplasmic body or *Nebenkörper* in contact with the nucleus, in some of the forms; the granular protoplasm; the differentiation of the ectoplasm and endoplasm; the blunt pseudopodia). At 12 is shown a form containing a red blood corpuscle. Nos. 14, 15 and 16 are examples of the encysted stage, showing the division of the nucleus and cytoplasmic body into the swarm spores; 17, young parasites just after leaving the cyst. Some show a short flagellum while others do not show the flagellum. Nos. 18 and 19 are developing flagellate forms of *Paramoeba hominis*, showing the flagellum, nucleus, and cytoplasmic body; 20, fully developed flagellate forms, one of which is undergoing longitudinal division; 21, flagellate forms just after the disappearance of the flagellum, one of which already shows the typical amebic stage.

in shape, and having a refractive nuclear membrane. The cytoplasmic body, or *Nebenkörper*, may also be visible, in contact with the nucleus. Both soon disappear, however, and the cyst becomes filled with refractive dots or granules, due to the division of the cytoplasmic body and the nucleus, and these eventually take part in the formation of the young flagellates or swarm-spores. At a later stage of development the cysts appear to be crowded with small spherical bodies, rather refractive in nature, which sometimes appear to move about within the cyst wall, but I have been unable, as yet, to be sure of this observation, as the motion is very limited and may be molecular in nature. At the very latest stage of development within the cyst, the outline of the young flagellates may be distinguished, most of them appearing spherical in shape and a dull gray in color. I have not been able to stain the cystic forms.

### 3. *The Flagellate Stage.*

I have not been able to observe the escape of the young flagellates from the cyst in which they have developed, but groups of these organisms are frequently observed, surrounded by cellular detritus and the ruptured cyst-wall, and arranged in spherical masses corresponding in size with the original cyst. These organisms very evidently have developed within the cysts, and soon assume the typical appearance presented by the flagellate stage of this parasite.

At first the young swarm-spores do not appear to possess a flagellum and are very small, measuring from 3 to 6 microns in diameter; they are spherical in shape, and have a finely granular protoplasm, in which the nucleus is not well differentiated. If one watches these young amebas for a while, it will be observed that one by one they become motile, a very delicate flagellum appearing at some portion of the periphery; they disengage themselves from the material in which they appear to be embedded, and move forward in a rapid, jerky manner, propelled by the flagellum, which thus appears to be situated posteriorly. The very young forms do not stain well with any of the stains mentioned above.

The organisms grow rapidly and when fully developed the flagellates measure from 10 to 20 microns in diameter. They are circular in shape, except at the portion of the periphery where the flagellum is attached. The flagellum is from three to four times as long as the diameter of the parasite, and tapers very rapidly, the outer three-fourths of the flagellum being so extremely delicate as to require the most careful focusing to demonstrate it. At the point of attachment of the flagellum to the body of the parasite it appears to be continuous with the protoplasm, and the nucleus, in most instances, is situated near this portion of the organism.



The flagellum appears to be situated posteriorly; the organism apparently is propelled forward by its lashing movements, but sometimes is observed moving with the flagellum forward.

The protoplasm of the organism at this stage of development appears very finely granular and contains a small, but well defined nucleus, and a minute cytoplasmic body, the *Nebenkörper* of Schaudinn. The nucleus is spherical in shape, and has a delicate, refractile nuclear membrane. The cytoplasmic body lies in contact with the nucleus, appearing as a somewhat refractile body, measuring about 2 microns in diameter. The protoplasm rarely may contain one or two red blood corpuscles, so that it is evident that the property of engulfing these cells is not confined to the amebic stage of development.

At the time of my original description I had not been able to observe the reproduction of these flagellate forms, but since then I have observed longitudinal division in the flagellate stage of development. Organisms may be observed in which there are present two nuclei and one can see the partial division of the flagellum into two portions. That these forms are not conjugating organisms is proved by the fact that the division of the nucleus may be observed before there is any division of the flagellum, the organism at this stage showing two nuclei and but one flagellum. It is probable that the division of the nucleus is preceded by the division of the cytoplasmic body or *Nebenkörper*, but I have not been able to satisfy myself that this is so. After division of the nucleus the protoplasm divides longitudinally, as well as the flagellum.

After reproducing in this way for a while the flagellum is lost, and the organism enters on its amebic stage of existence.

The flagellate stage stains poorly with the stains mentioned. Rarely with Wright's stain I have been able to get a differentiation between the protoplasm and the nucleus, the protoplasm staining a deep blue, and the nucleus a deep crimson or violet. The cytoplasmic body stains almost black and is generally not well differentiated.

#### PATHOGENICITY

I have not been able to determine experimentally the question of the pathogenicity of *Paramaba hominis*, but from the clinical symptoms present in the patients harboring the parasite, and the fact that recovery followed the disappearance of the parasite, I believe that it is justifiable to conclude that it may cause a form of chronic diarrhea occurring in the tropics, and characterized by exacerbations of acute diarrhea alternating with periods of constipation. All of the patients whom I found infected with this parasite, lived in, or had served in the Philippine Islands. Of

the nine cases, six were Filipinos, and three American soldiers. All of them were suffering from diarrhea at the time the organism was found in their feces, although in one instance the condition was complicated by a severe dysentery due to *Entamoeba histolytica*. Omitting this case, we have eight patients in whom the presence of *Paramoeba hominis* was accompanied by the usual symptoms of a severe diarrhea, and all gave a history of having suffered from several such attacks, alternating with periods of constipation. In five of the patients the feces contained a small amount of blood and mucus, while in two *Trichomonas hominis* was present in small numbers. It will thus be seen that in eight of the cases *Paramoeba hominis* was the only protozoon present which could be looked on as of possible etiological significance, the two patients showing trichomonads having them in too small number to suggest any relation between the trichomonads and the symptoms present. Treatment by irrigation of the bowel resulted in the disappearance of the parasites, and, with them, of the diarrhea, and none of the patients have relapsed, so far as I have been able to determine. Thus the evidence, so far as it goes, points to *Paramoeba hominis* as the cause of the diarrhea, and I believe that we may safely regard this parasite as belonging to the pathogenic protozoa.

#### DIFFERENTIAL DIAGNOSIS

In the amebic stage of development *Paramoeba hominis* may be confused with *Entamoeba coli*, *Entamoeba histolytica*, or *Entamoeba tetragena*. If it be remembered that the endoplasm of this species is more refractive than is the ectoplasm, it will be easy to differentiate it from the other intestinal amebas. The occurrence of the peculiar cysts and of the flagellate stages of development at the same time, however, should enable one to diagnose this species of ameba with but little difficulty. The process of encystment which I have described as occurring in this species is peculiar to it, and whenever one observes the rotating organisms one may be sure that *Paramoeba hominis* is present.

In the flagellate stage of development the only organism occurring in the feces which might be confused with *Paramoeba hominis* is *Trichomonas hominis*, because of certain peculiarities in its development. The latter organism is frequently observed in the resting stage, when it is spherical in form, and appears to possess a limited degree of ameboid motion. It is much smaller, however, than *Paramoeba hominis*, and never shows the active progressive ameboid motility observed in the latter. The flagellate stage of *Paramoeba hominis* is distinguished from the active *Trichomonas hominis* by the absence of an undulating membrane, the presence of but one flagellum, and the spherical form of the organism.

The occurrence in the feces of the amebic stage, the encysted stage, and the flagellate stage of *Paromaba hominis* is characteristic of this organism, and no difficulty should be experienced, by one who is used to making examinations of the feces, in differentiating this species from the other intestinal protozoa.

In conclusion I would again call attention to the possible occurrence of this parasite as a causative agent in the chronic diarrheas frequently observed in certain regions of the United States, especially in the Southern states, and would suggest the value of a careful examination of the feces in all such instances.

# THE QUANTITATIVE DETERMINATION OF THE CHLORIDS IN THE URINE\*

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The methods commonly described for the determination of the chlorids in the urine are, with the exception of those of Mohr and Volhard, either too long and complicated for the busy clinician or too inaccurate for anything approaching scientific work.

The method described by Mohr,<sup>1</sup> in which the chlorids are precipitated by a standardized solution of silver nitrate, using potassium chromate as an indicator, is a rapid and convenient process. It uniformly gives too high results,<sup>2</sup> however, as the silver also precipitates the uric acid, purin bases, urinary pigments, etc., and therefore is not satisfactory for accurate work in the urine.

The Volhard method<sup>3</sup> as modified by Drechsel<sup>4</sup> and applied to the urine by Falek and Arnold consists briefly in the precipitation of the chlorids by an excess of a standardized solution of silver nitrate, the removal of the silver chlorid by filtration and titration of the excess of silver nitrate with a standardized solution of ammonium thiocyanate, using an iron salt as an indicator. This method is very accurate but requires about thirty minutes for duplicate analyses on a specimen, necessitates the use of volumetric flasks, which are not always at hand and involves considerable manipulation, thus introducing a possible source of error in the hands of the clinician.

The original method as described by Volhard in 1874 is much shorter, as it does not require the removal of the silver chlorid by filtration, the titration with the ammonium thiocyanate being done in its presence. Drechsel, attempting to use this method, found difficulty with the end point and was unable to obtain accurate results, owing, as he thought, to the precipitated silver chlorid reacting with the ammonium thiocya-

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\* From the Sheffield Laboratory of Physiological Chemistry and the Medical Laboratory of Yale University.

1. Mohr, F.: *Lehrbuch der Titrimethode*, 1856, 11, 13.

2. Neubauer and Vogel: *Anleitung zur Analyse des Harns*, 1898, p. 709.

3. Volhard, J.: *Ueber eine neue Methode der massanalytischen Bestimmung des Silbers*, *Jour. f. prakt. Chem.*, 1874, ix, 217.

4. Drechsel, E.: *Zur Volhard'schen Silberbestimmung*, *Jour. f. prakt. Chem.*, 1877, xv, 191.

nate. To obviate this he introduced the step of filtration. The necessity of this has since then been emphasized by several investigators and this step is now commonly accepted and described with the test. Recently, in support of this view, Rosanoff and Hill<sup>5</sup> have reported a series of experiments in which they found that shaking equivalent amounts of freshly precipitated silver chlorid and a solution of ammonium thiocyanate together for two minutes brought about an interaction involving 43 per cent. of the latter.

In opposition to this view several observers have stated that this step is not necessary and that it is possible to obtain accurate results according to the original method. The most recent report is that of Goodall,<sup>6</sup> who has made a comparative study of sixty urines of widely varying chlorid contents, in which he used both the modified Volhard and the original Volhard method. The largest variation found by him, using the modified Volhard as a standard, was 0.3 gm. sodium chlorid in a day's output of 25.7 gm., the average difference for the sixty urines being less than 0.1 gm., which is within the error of the usual clinical apparatus.

In making a number of chlorid determinations in urine according to the original Volhard method, I noticed that when only a small amount of nitric acid was used, the end point was indistinct and that it was difficult to obtain duplicates. On increasing the amount of acid used, however, the end point became sharp and two determinations on the same urine checked within the error of reading the burette. Moreover, on comparing these results with those obtained with the modified Volhard they were found to be identical.

The explanation of the effect of the nitric acid on this end point and its connection with the reaction between the precipitated silver chlorid and the ammonium thiocyanate as described by Rosanoff and Hill involves a study of the chemical reactions taking place during the process of this determination. The chlorids are first precipitated by silver nitrate, the excess of the latter being titrated with ammonium thiocyanate. The reaction between the silver nitrate and the ammonium thiocyanate is practically instantaneous, while that between the silver chlorid and the cyanate is comparatively slow, as shown by Rosanoff and Hill (43 per cent. of the ammonium thiocyanate involved in two minutes). Therefore the latter reaction will not take place until all the

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5. Rosanoff, M. A., and Hill, A. E.: A Necessary Modification of Volhard's Method for the Determination of Chlorids, *Jour. Am. Chem. Soc.*, 1907, xxix, 269.

6. Goodall, H. W.: An Accurate Method for the Quantitative Determination of Chlorin in Urine, *Boston Med. and Surg. Jour.*, 1909, clx, 304.

silver nitrate is precipitated. When this point is reached a third factor comes into play: the ferric alum used for the indicator. This undoubtedly forms with the thiocyanate a certain amount of undissociated ferric thiocyanate, as is shown by the red color which is due to the presence of the undissociated salt. This reaction lowers the amount of thiocyanate free to react with the silver chlorid and the reaction between the silver chlorid and the thiocyanate would therefore proceed more slowly than would be the case if the alum were absent. To show that the reaction is retarded in the presence of alum the following experiments were performed:

Equivalent amounts of freshly precipitated silver chlorid and ammonium thiocyanate were stirred together at approximately the same rate as in doing the determination, for two minutes, in the presence of the amounts of a saturated solution of ferric ammonium sulphate stated in Table 1. The results are expressed as the per cent. of the ammonium thiocyanate reacting with the silver chlorid. For a description of the method of determining the amount of this reaction consult Rosanoff and Hill.<sup>5</sup>

TABLE 1.—REACTION BETWEEN SILVER CHLORID AND AMMONIUM THIOCYANATE WITH AND WITHOUT FERRIC AMMONIUM SULPHATE

Experiment.	Amount of Iron Used. c.c.	Per Cent $\text{NH}_4\text{CNS}$ Reacted With.	Average Per Cent.
Rosanoff and Hill..... 1	0	45.6	....
Rosanoff and Hill..... 2	0	43.1	....
Rosanoff and Hill..... 3	0	41.3	43.3
Harvey ..... 1	0	44.9	....
Harvey ..... 2	0	41.6	....
Harvey ..... 3	0	45.7	44.0
Harvey ..... 1	2.5	28.0	....
Harvey ..... 2	2.5	30.0	29.0
Harvey ..... 1	4.0	22.5	....
Harvey ..... 2	4.0	25.8	24.1

From these results it is seen that the reaction taking place between the silver chlorid and the ammonium thiocyanate under the conditions in which the determination is usually performed, that is, in the presence of the iron salt, is over 40 per cent. less than that stated by Rosanoff and Hill, in the absence of the iron alum.

That the nitric acid has a similar effect on this reaction is borne out by the following experiments performed in the same manner as those above, using nitric acid in place of the ferric indicator.

TABLE 2.—REACTION BETWEEN SILVER CHLORID AND AMMONIUM THIO-CYANATE WITH AND WITHOUT NITRIC ACID

Experiment.	Amount of Nitric Acid Used, c.c.	Per Cent $\text{NH}_4\text{CNS}$ Reacted With.	Average Per Cent.
Rosanoff and Hill..... 1	0	45.6	....
Rosanoff and Hill..... 2	0	43.1	....
Rosanoff and Hill..... 3	0	41.3	43.3
Harvey ..... 1	0	44.9	....
Harvey ..... 2	0	41.6	....
Harvey ..... 3	0	45.7	44.0
Harvey ..... 1	1.0	32.6	....
Harvey ..... 2	1.0	33.7	....
Harvey ..... 3	1.0	33.3	33.2

The failure to appreciate the part that the nitric acid plays in this determination and to realize its importance may, I think, suffice to explain the widely differing results obtained by different investigators in the past.

In order to determine the absolute error in relation to solutions containing known amounts of sodium chlorid and the relative error as compared with the modified Volhard, the following determinations were made by the original Volhard, using an excess of acid.

Five c.c. of the salt solutions were taken and a solution of silver nitrate, of which 1 c.c. was equivalent to 0.01 gm. of sodium chlorid. Further details as to the method and the solutions used may be found in the detailed description of the method given below.

TABLE 3.—DETERMINATIONS BY ORIGINAL AND MODIFIED VOLHARD METHODS

Method.	Exp.	Known Amount of NaCl in 100 c.c.	Determined Amount of NaCl in 100 c.c.	Diff. in gm.	Per Cent. Error.
Volhard, orig.....	1	0.7039	0.7050	+0.0011	0.15
Volhard, orig.....	2	0.7039	0.7010	—0.0029	0.41
Volhard, orig.....	3	0.7039	0.7050	+0.0011	0.15
Volhard, orig.....	4	0.7039	0.7034	—0.0005	0.07
Volhard, orig.....	5	0.7039	0.7074	+0.0035	0.49
Volhard, orig.....	6	0.7039	0.7094	+0.0055	0.78
Average.....	..	0.7039	0.7052	+0.0013	0.18
Volhard, mod.....	1	0.7039	0.7100	+0.0061	0.86
Volhard, mod.....	2	0.7039	0.7030	—0.0009	0.12
Average.....	..	0.7039	0.7065	+0.0026	0.36
Volhard, orig.....	1	0.6332	0.6350	+0.0018	0.28

TABLE 3.—Continued

Method.	Exp.	Known Amount of NaCl in 100 c.c.	Determined Amount of NaCl in 100 c.c.	Diff. in gm.	Per Cent. Error.
Volhard, orig.....	2	0.6332	0.6376	+0.0044	0.69
Volhard, orig.....	3	0.6332	0.6390	+0.0058	0.91
Volhard, orig.....	4	0.6332	0.6320	—0.0012	0.19
Average.....	..	0.6332	0.6359	+0.0027	0.42
Volhard, mod.....	1	0.6332	0.6380	+0.0048	0.75
Volhard, mod.....	2	0.6332	0.6360	+0.0028	0.44
Volhard, mod.....	3	0.6332	0.6340	+0.0008	0.12
Volhard, mod.....	4	0.6332	0.6400	+0.0068	1.07
Average.....	..	0.6332	0.6370	+0.0038	0.60

In order to supplement Goodall's results in urines, the following determinations were made by the original Volhard, using the indicator and nitric acid solution as described below. Five c.c. of the urines were taken, the other solutions being the same as in the preceding experiment.

TABLE 4.—DETERMINATIONS BY ORIGINAL AND MODIFIED VOLHARD METHODS

-----Volhard mod.-----				-----Volhard orig.-----			
Urine.	Amount AgNO <sub>3</sub> Used.	Gm. NaCl 1200 c.c.	Average.	Amount AgNO <sub>3</sub> Used.	Gm. NaCl 1200 c.c.	Average.	Diff. in gm.
1	7.00	16.80	.....	7.00	16.80	.....	.....
	7.05	16.92	16.86	7.02	16.87	16.82	—0.04
2	2.80	6.72	.....	2.85	6.84	.....	.....
	2.83	6.79	6.75	2.82	6.77	6.80	+0.05
3	8.40	20.16	.....	8.42	20.20	.....	.....
	8.45	20.28	20.22	8.42	20.20	20.20	—0.02
4	8.30	20.92	.....	8.30	19.92	.....	.....
	8.37	20.08	20.00	8.35	20.04	19.98	—0.02

The time taken to do the duplicate analyses on a urine, according to the modified Volhard, was from twenty-five to thirty minutes; with the original Volhard method from five to six minutes.

The method finally adopted as a result of these experiments requires the following solutions. The first two of these are commonly described in connection with the Volhard determination in all standard books on laboratory methods.

1. A silver nitrate solution containing 29.042 gm. of chemically pure, crystalline, silver nitrate in one liter of distilled water; 1 c.c. of this solution is the equivalent of 0.01 gm. of sodium chlorid.



2. A solution of ammonium thiocyanate, 20 c.c. of which is equivalent to 10 c.c. of the silver nitrate solution. As this salt is very hygroscopic, it cannot be weighed out with sufficient accuracy to make up the solution directly. Therefore 13 gm. of it are dissolved in one liter of distilled water, thus making a concentrated solution, whose strength is determined by titration against the silver nitrate solution and the requisite dilution made.

This is done in the following manner: 10 c.c. of the silver nitrate solution are pipetted into a beaker, diluted with 30 to 50 c.c. of distilled water, 2 c.c. of the indicator added and the whole titrated with the ammonium thiocyanate solution. The total amount of the concentrated cyanid solution is divided by ten, reading in the above titration, and the result multiplied by the difference between this reading and 20 c.c. This will give the amount of distilled water to be added to the concentrated solution to bring it to the desired strength.

3. The indicator containing nitric acid. To 30 c.c. of water are added, first, 70 c.c. of nitric acid (sp. gr. 1.2, or 33 per cent); then 100 gm. of crystalline ferric ammonium sulphate are dissolved in this menstruum and filtered. This makes a strong nitric acid solution which is saturated with the iron salt.

This indicator is recommended inasmuch as it substitutes the one solution in place of the two (the ferric indicator and the acid) and insures the use of a proper amount of the acid. Moreover, it is sufficiently concentrated so that it is necessary to use only 2 c.c. and therefore it may be conveniently kept in a small reagent bottle. The stopper of this bottle may be a graduated dropper which can at the same time serve to measure and transfer the indicator.

To perform the determination 5 c.c. of the urine are pipetted into a small beaker and diluted with about 20 c.c. of distilled water. The chlorids in this solution are now precipitated with exactly 10 c.c. of the silver nitrate solution and about 2 c.c. of the acidified indicator added. The ammonium thiocyanate is then run in from a burette until the first trace of red shows throughout the mixture. On allowing the precipitate to settle out, this may easily be recognized in the supernatant fluid. If, however, the mixture is stirred violently the color will disappear. When the end point appears on the addition of the first drop of the ammonium thiocyanate solution, then 10 c.c. more of the silver nitrate are to be added and the titration completed with corresponding allowance in the calculation.

The calculation is simple and may be done in either of two ways. The first is as follows: As 20 c.c. of the ammonium thiocyanate solution

is equivalent to 10 c.c. of the silver nitrate, divide the difference of the readings on the burette by two and subtract the quotient from 10 c.c., the amount of silver nitrate taken. The result is the number of cubic centimeters of silver nitrate solution actually used in the precipitation of the chlorids. As 1 c.c. of the silver nitrate solution is equivalent to 0.01 gm. of sodium chlorid, the number of cubic centimeters of silver nitrate solution used multiplied by 0.01 gm. will give the amount of sodium chlorid in 5 c.c. of the urine, the quantity taken. The total amount of the urine on which the chlorid content is to be determined is to be divided by 5 c.c. (the sample taken), and the amount of sodium chlorid in 5 c.c. of the urine multiplied by this figure. The result expresses the total content of sodium chlorid.

A second method, somewhat shorter, is to subtract the burette reading from 20 c.c., multiply this by the total volume and point off three places. The final result will be the same as derived by the former method.

#### SUMMARY

1. In the Volhard method for the determination of chlorids in the urine, the precipitated silver chlorid does not react with the ammonium thiocyanate in the presence of an excess of silver nitrate.

2. The reaction between the precipitated silver chlorid and the ammonium thiocyanate is markedly depressed by the presence, first, of the ferric salt; and, secondly, of an excess of nitric acid.

3. The relative sharpness of the end point in this determination is dependent on the presence of an excess of nitric acid. By its use the step of filtration becomes superfluous.

4. The time required to do duplicate determinations by this method is from five to six minutes, as compared with twenty-five to thirty minutes by the usual method.

5. A convenient acidified ferric indicator is described, which insures the use of the proper amount of acid.

6. Results obtained according to this method are of the same degree of accuracy as those obtained by the usual modified Volhard method.

I am deeply indebted to Professor Lafayette B. Mendel and Assistant Prof. H. W. Foote for criticism and invaluable suggestions in the preparation of this paper.

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## THE BOVINE TYPE OF TUBERCULOSIS ASSOCIATED WITH THREE CASES OF TUBERCULOSIS IN MAN\*

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Practically all cases of human tuberculosis with which the bovine type of bacillus has been found associated have had their origin in the digestive tract. The invasion takes place either through the mouth or throat into the cervical lymph-nodes, or through the intestinal mucosa into the mesenteric lymph-nodes. Although the infection of cows takes place largely through the air, and first shows itself in the mediastinal or bronchial lymph-nodes, yet there is at present no evidence that adult human beings exposed to the dust of cow-stables contract tuberculosis in this way. The three cases to be briefly reported are also the result of intestinal infection.

### REPORTS OF CASES

CASE 1 (Human No. 25).—For the autopsy notes and material of this case I am indebted to Prof. E. E. Southard, who also supplied the following data concerning the history of the patient:

*Patient.*—Man, born in Massachusetts, in 1888, of Nova Scotian parents. Became epileptic in 1893. Was admitted to Danvers Hospital in March, 1906; there showed paraplegia, epilepsy and dementia; broke right humerus and right femur in different convulsive attacks, and died Oct. 28, 1908, after a series of convulsions of increasing frequency which developed into status epilepticus lasting twenty-four hours. During his stay in the hospital the patient drank raw milk daily. His mother began to show signs of pulmonary tuberculosis in 1896, but was still alive in 1906, when he was admitted.

*Autopsy.*—The following facts are of interest to us in the autopsy: Body was that of a rachitic individual 120 cm. in length. (Barrel chest, rachitic rosary, anomalies of skull development, and distortion of the long bones.) Scars on the forehead. Pupils unequal, left larger than right.

Mesenteric lymph-nodes swollen and slightly reddened. One near the colon contained a calcified mass 1.5 cm. in diameter. Chronic perisplenitis.

Pleural cavities show chronic adhesions over the left lower lobe and a persistent thymus.

Lungs free of apical scars; were merely edematous. Lymph-nodes not enlarged.

Heart of normal size. Few sclerotic patches in the coronaries. Slight acute splenitis and fatty liver.

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\* From the Department of Comparative Pathology, Harvard University Medical School.

1. These numbers correspond to the serial numbers used in the Department of Comparative Pathology, Harvard Medical School, by Prof. Theobald Smith.

Brain: Weight 1.115 gm. Dura slightly adherent and thickened. Recent fibrinous adhesions to pia. Subpial fluid opaque; convolutions flattened.

*Anatomic Diagnosis.*—This is given as a questionable acute cerebrospinal meningitis with persistent thymus and various chronic conditions, among which may be mentioned chronic adhesive pleuritis; chronic tuberculous lymphadenitis (mesenteric) with calcification; chronic adhesive perisplenitis.

*Bacteriologic Cultures.*—The mass of lymph-nodes which formed the starting-point of the cultures was the only manifest tuberculous focus in the body. The nodes were evidently enlarged and permeated with inconspicuous caseous foci. The method usual in this laboratory was resorted to with material of this kind. It was cut up and ground as much as possible in a sterile agate mortar with salt solution and the turbid fluid injected into the peritoneal cavity of two guinea-pigs. Both became tuberculous, but only one was used for cultures. The method we have found most reliable for coaxing into active growth tubercle bacilli which are cultivated with difficulty is to put bits of tissue as large as peas, usually from the spleen, into Dorset's egg medium, and after from six to eight weeks to spread the masses of growth as well as the original tissue thoroughly over the surface of fresh egg and glycerin agar tubes. This transfer is repeated until a fairly good growth is obtained on glycerin agar, when the egg medium is abandoned. The other medium most commonly employed—beef serum—is less certain and cultures may be lost. The best medium—dog serum—is obtained with difficulty, and therefore not used at present.

Inasmuch as the morphology of the tubercle bacillus is more or less influenced by the culture medium used, only coagulated serum should be used for comparative studies. On glycerin agar involution forms soon appear to complicate the morphologic picture.

In the present case, after the third transfer on egg medium, representing a total period of growth of over five months, a glycerin agar culture was obtained from which a series of successful subcultures have been carried on. There are at present four tests which taken together enable us to classify mammalian bacilli into the human and the bovine type. These refer to:

1. The form of the bacilli.
2. The dysgenetic or eugenetic characters of the culture according to the terminology employed by the Royal Commission of England.
3. The relative virulence toward rabbits.
4. The reaction curve in 5 per cent. glycerin bouillon.

Culture Human 25 was dysgenetic for the usual time, although at present, about eighteen months after isolation, it is nearly as vigorous as the human type. This strain was virulent for rabbits, as indicated in Table 1, and in its reaction curve it corresponds closely to that of the bovine type, as shown in Table 2. Concerning this table it should be stated that the cultures there given were chosen because they were prepared simultaneously from the same lot of bouillon and were made in every respect under identical conditions.

CASE 2 (Human No. 26).—For the clinical history and the autopsy notes I am indebted to Dr. L. J. Rhea of the Department of Pathology of the Harvard Medical School.

*Patient.*—The case was that of an infant. Up to February, 1909, there had been no illness. At that time an acute but slight illness appeared, thought to be bronchitis. Thereafter the child was only comparatively well, but at no time actually ill. Temperature records are lacking. Death occurred in April, after symptoms of acute nephritis. There was no source of the tuberculous infection traceable to the immediate environment of the child. The autopsy in this case is definite and perhaps the anatomic diagnosis will be sufficient.

TABLE 1.—INOCULATION OF RABBITS

Designation of Culture.	Total Age.	Number of Transfers.	Age of Culture Used, in Days.	Dose Inj. into Vein of Ear.	Number of Rabbit.	Initial Wt.	Final Wt.	Result.	Remarks.
Human 25	9½ mos.	6	35	0.5	382	1870	1280	Killed after 39 days because animal dying.	Extensive tuberculosis of lungs, many minute tubercles in cortex of kidneys and wall of cecum and colon. Many minute grayish tubercles in lungs, liver, spleen and kidneys.
Human 26	4 mos.	2	35	0.5	377	2130	2340	Killed in 34 days as dying in state of severe dyspnea.	
Human 27	20 days	1	20	3.0* abdomen	368	?	2240	Died in 33 days.	Extensive tuberculosis of peritoneum and lungs. (Acute military tuberculosis.)

\* Very dilute suspension.

TABLE 2.—CULTURES OF TUBERCLE BACILLI IN BOUILLON

Bouillon Composition of.	Designation of Culture.	Date of Inoculation.	Total Age of Culture, Months.	Reaction of Bouillon in Per Cent. of a Normal Solution After:	Alkaline.	
Yeast infusion plus 1 per cent. peptone (Witte), 0.5 per cent. salt and 5 per cent. glycerin; reaction 2.00 per cent. of a normal acid layer 1.5 cm. deep in 100 c.c. Erlenmeyer flask.	Human 25	11 19 09	11 2/3	(a) 41 days (b) 62 days	0.5 (a) 80 days 0.25 (b) 91 days	1.00*
	Bovine 10	11 19 09	18 1/2	(a) 41 days (b) 62 days	0.12 (a) 91 days 0.00 (b) 80 days	0.25 0.12
	Human (1)	11 19 09	?	(a) 41 days (b) 63 days	0.87 (a) 80 days 0.0137 (b) 91 days	0.12 2.75 3.25

\* Continued for 24 days.

\* Contaminated with another bacillus.

† Culture submitted for test. Had been passed through a cow several years before. Originally isolated from human being.

*Anatomic Diagnosis.*—Tuberculosis of the intestines and mesenteric lymph-nodes; tuberculosis of lungs, spleen, liver, and peritoneum; involvement of the bronchial glands. Judging by the stage of the disease, the process was oldest in the intestines, where there was ulceration, and in the mesenteric lymph-nodes, which contained creamy areas of softening. In the other organs the lesions had not advanced beyond the small discrete or confluent grayish, somewhat translucent, tubercles.

*Bacteriologic Cultures.*—The culture was isolated from a completely caseous, softened mesenteric lymph-node by passage through three guinea-pigs. Cultures were isolated from each guinea-pig in the manner indicated above, and all but one strain discarded after a time. The feeble growth on glycerin agar has continued up to the present, so that the reaction curve in glycerin bouillon has not yet been obtained, although the strain has been just one year under cultivation. Its virulence for rabbits is shown in Table 1. Altogether the strain must be regarded as of bovine origin.

CASE 3 (Human No. 27).—This strain has been under cultivation only a short time, but I venture to class it with the bovine type because of its very short form and its high virulence for rabbits.

*Patient.*—The clinical history of the case is as follows: A previously healthy baby girl had a convulsion when 16 months old. The attack was preceded by a few days of malaise. The child recovered slowly, showing some weakness of the limbs on the left side. Ten days later there was a second convulsion, the child remaining in a more or less comatose state until death, about a month from the first symptoms. The signs pointed to a meningitis, and a probable diagnosis of tuberculous meningitis was made. Lumbar puncture was performed and 30 c.c. of clear fluid obtained. An examination of the cellular elements of this fluid showed a marked increase of lymphocytes (85 per cent). The child died in a few days.

*Autopsy.*—The notes, for which I am indebted to Prof. E. E. Southard, were apparently quite negative with the exception of the brain.

The mesenteric lymph-nodes were described as numerous, fairly large, and in part considerably injected, but no node showed caseation or other focal lesion. Smears from these glands, however, did show tubercle bacilli.

Pleural cavities free from adhesions. Lungs congested; possibly an early pneumonic process. Bronchial lymph-nodes not remarkable.

Tonsils not obtained. No lesion noted clinically.

The brain substance bulged on removal of the calvarium. A thick exudate containing numerous tubercles covered the base. The pia mater contained numerous miliary and conglomerate tubercles having a rather characteristic vascular distribution. The prefrontal and the inferior parietal and occipital regions were freest of tubercles, the right inferior-frontal being most involved.

*Anatomical Diagnosis.*—Acute edema and congestion of the lungs; slightly injected mesenteric lymph-nodes; tuberculous meningitis.

*Bacteriologic Cultures.*—The material from which the cultures were ultimately obtained was the spinal fluid withdrawn during life by lumbar puncture and injected into the peritoneal cavity of two guinea-pigs. From these, cultures on egg media were made in the usual way. The growth was very slow, but after about seven weeks colonies were distinct, and a smear showed very short forms not exceeding one micron in length. As indicated in Table 1, a rabbit was inoculated with one of the first cultures from a guinea-pig on egg medium. At the date of the injection the growth was so feeble that in a smear from a suspension in normal salt solution only two clumps of bacilli were detected. A relatively large amount of this suspension was therefore injected into the peritoneal cavity

at a venture. The rapid death of the rabbit, the presence of myriads of tubercles on all peritoneal surfaces and a well-advanced generalized embolic tuberculosis of the lungs demonstrated a high virulence for rabbits. I do not hesitate, therefore, to range this culture with the bovine type, although a study of it is only partly under way.

These three cases illustrate three different types of tuberculosis, all obscure as to diagnosis during life. In the first case—that of an adolescent—either the local tuberculosis may have had no immediate connection with the cause of death, or else the beginning of dissemination of the virus from the primary focus may have led to a reaction of the tuberculin type and to death. In the second case—that of an infant—the generalized tuberculosis starting from the mesenteric lymph-nodes was evidently not suspected, for the clinical history states that within the last week of life the patient had an acute illness of an indefinite type, which culminated in symptoms of acute nephritis. Here also the liberation of tubercle toxins may have been responsible for the acute nephritis.

In the third case—that of a child of seventeen months—the symptoms pointed to the central nervous system and at one time a tentative diagnosis of anterior poliomyelitis was made.

In conclusion it should also be stated that no similar cases have come under observation during this period. They may be considered three consecutive cases as studied in this laboratory, all due to the bovine type of tubercle bacillus.

# A STUDY OF THE NITROGEN AND SULPHUR METABOLISM IN MORBUS CERULEUS

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The polycythemia associated with cardiac disease is to be regarded as a conservative process, wherein the increase in the number of oxygen-carrying cells compensates more or less for the imperfect circulation resulting from obstruction to the blood-stream, or admixture of venous with arterial blood. The observations of Weil<sup>1</sup> favor this conception of erythrocytosis, and the experiments of Seller,<sup>2</sup> who induced polycythemia in animals by reduction of the oxygen tension of the inspired air, indicate that bone-marrow reacts physiologically to partial asphyxia, by hyperplasia and increased cell output.

In certain cases of congenital cardiac defect, the remarkable grade of cyanosis would suggest that, in spite of the increase in the number of erythrocytes, the tissues are not perfectly supplied with the adequate amounts of oxygen, inasmuch as the cyanosis is here due to the venous character of the blood in superficial capillaries. Lepine<sup>3</sup> found as high as 64 per cent. of carbon dioxid in the venous blood in a case of obstructive heart-disease. The slowing of the blood in the capillaries leads to a more rapid diffusion of the oxygen into the tissues and of the carbon dioxid into the blood.

We have, then, in conditions of this sort, an apparent tissue suffocation notwithstanding the compensatory increase in the number of erythrocytes in the blood; and it seemed interesting to investigate the effect, if any, that a possibly lowered oxygen tension in the tissues might induce on the nitrogen and sulphur metabolism.

The history of the subject of this study need not be given in detail. He is 7 years of age. At birth he was a "blue baby" and has always been in delicate health, but has been fortunate enough to evade all the diseases of childhood. On account of the dyspnea excited by the activities common to children, he has learned to amuse himself in other ways and this was made more easy by an unusually active mind—an exceptional association with congenital cardiac defect. Ordinarily he is comfortable and

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1. Weil: *Compt. rend. Soc. de biol., Paris*, 1901. liii. 713.

2. Seller: *Thèse de Bordeaux*, 1896.

3. Quoted from Adami and Nicholls, *Principles of Pathology*, 1909. ii. 29.



TABLE I. NITROGEN EXCRETION

Date, 1909, Nov.	Volume Urine, cc.	Total Nitrogen.	Urea Nitrogen.	Treat.	Ammonia Nitr <sup>o</sup> - gen.	Uric Acid Nitr <sup>o</sup> - gen.	Uric Acid.	Creatinin.	Nitr <sup>o</sup> - gen.	Creatinin.	Rest. Nitrogen.	In Per Cent. of Total Nitrogen			
												Treat.	Ammonia.	Uric Acid.	Creatinin.
Eight	430	60.35 mg.	11.42 mg.	72.7	0.1	0.066	0.206	0.040	0.840	0.030	0.20	8.8	1.4	1.7	1.1
Ninth	430	60.35 mg.	11.42 mg.	72.7	0.1	0.066	0.206	0.040	0.840	0.030	0.20	8.8	1.4	1.7	1.1
Tenth	430	60.35 mg.	11.42 mg.	72.7	0.1	0.066	0.206	0.040	0.840	0.030	0.20	8.8	1.4	1.7	1.1
Eleventh	390	56.92	10.66	59.5	0.1	0.066	0.206	0.040	0.840	0.030	0.20	8.8	1.4	1.7	1.1
Twelfth	330	55.75	10.66	59.5	0.1	0.066	0.206	0.040	0.840	0.030	0.20	8.8	1.4	1.7	1.1
Thirteenth	320	50.53	10.66	59.5	0.1	0.066	0.206	0.040	0.840	0.030	0.20	8.8	1.4	1.7	1.1
Fourteenth	330	55.75	10.66	59.5	0.1	0.066	0.206	0.040	0.840	0.030	0.20	8.8	1.4	1.7	1.1

\* Nitrogen determined by

Kjeldahl's method; urea, ammonia and creatinin by method of Folin; uric acid by Folin-Schaffer method

appears to enjoy life, but at times, following undue exertion or on contracting a cold, there are severe paroxysms of pain in the chest and abdomen. At these times, the cyanosis is more intense even than usual. The child is under normal size, weighing 17 kilos. The striking feature in his appearance is the deep grade of cyanosis; the lips and mucous membranes are livid, the skin and the extremities dusky. (It is notable that during sleep the cyanosis often almost completely disappears so that one would scarcely imagine the change produced a few moments after waking). There is a prominence of the eyes suggesting exophthalmos. The ends of the fingers are "clubbed" and the hands and the feet are always cold to the touch.

There is nothing in the physical examination of the heart to lead to accurate diagnosis. The heart is not enlarged, there are no murmurs characteristic of valvular disease and, while the accentuation of the first and second sounds is not quite normal, it gives no clue to the nature of the abnormality. The erythrocytes average 12,900,000 per c.mm.

The diet used during the research period consisted of cereals, bread and butter, milk and eggs. This is about the normal diet for this child, since he does not care for meat and eats it only when urged to do so.

In Table 1 the results of the analysis of urine are given in respect to the nitrogen fractions. It will be noted that, although the total nitrogen is quite small in amount, the urea, ammonia, and undetermined nitrogen constitute normal percentages of the total. Of special interest, perhaps, is the creatinin excretion averaging 47 mg. pro diem, or, expressed as a creatinin coefficient, 2.7 mg. per kilo.

TABLE 2.—SULPHUR EXCRETION

Date.	Total Sulphur.	Total Sulphates.	Inorganic Sulphates.	Etherial Sulphates.	Neutral Sulphur.	In Per Cent. of Total S.	Per Cent. of Total S.	Neutral.
1909, Nov	Gm.	Gm.	Gm.	Gm.	Gm.	Inorg.	Ether.	Neut.
Eighth . . . . .	0.55	0.42	0.41	0.01	0.13	74.5	1.8	23.6
Ninth . . . . .	0.48	0.38	0.35	0.03	0.10	72.9	6.2	20.8
Tenth . . . . .	0.78	0.49	0.45	0.04	0.29	57.6	5.1	37.1
Eleventh . . . . .	0.52	0.41	0.39	0.02	0.11	75.0	3.8	21.1
Twelfth . . . . .	0.63	0.50	0.47	0.03	0.13	71.6	4.7	20.6
Thirteenth . . . . .	0.67	0.54	0.50	0.04	0.13	74.6	5.9	19.4
Fourteenth . . . . .	0.59	0.52	0.48	0.04	0.07	81.3	6.7	12.0
Average . . . . .	0.60	0.48	0.43	0.03	0.14	72.9	4.6	22.0
CONTROL								
1910, Jan.								
First . . . . .	0.75	0.62	0.60	0.02	0.13	80.0	2.6	17.3
Second . . . . .	1.05	0.95	0.87	0.08	0.10	82.8	7.6	9.5
Third . . . . .	1.20	1.15	1.08	0.07	0.05	90.0	5.8	4.1
Fourth . . . . .	0.68	0.63	0.60	0.03	0.05	88.2	4.4	7.3
Average . . . . .	0.92	0.84	0.79	0.05	0.08	85.3	5.1	9.5

Any error of metabolism, having its origin in deficient oxygen in the tissues, would be more apparent in the form of sulphur excretion than in the nitrogen. In Table 2 are given the figures for the urinary sulphurs,<sup>4</sup> along with a control.<sup>5</sup>

An especial interest is attached to the amounts of neutral sulphur since the sulphur-carrying bodies, grouped together under this name, have been shown to be relatively independent of the amounts of the sulphates found in urine<sup>6</sup> and are, to some degree at least, an index of the protein tissue metabolism. In this respect, these bodies are analogous to creatinin. Hence, it would be in the amounts of neutral sulphur that evidence might be found for abnormalities dependent on a lowered oxygen tension in the tissues. With the exception of one day, November 10, the amounts of neutral sulphur correspond fairly well with those of the control. It happened that on this day the patient had one of those attacks of "cramps," associated with evidences of embarrassed heart action which have been referred to above. Whether on the day in question there was any causal relation between the poor heart action and the high neutral sulphur cannot be definitely stated. Nevertheless, on the other days, there is not sufficient difference between the neutral sulphur of the patient and the control to give basis for the assumption of a pathological state.

We have then, in this instance, either a complete compensation for the defective heart in the erythrocytosis, so that the tissues receive as much oxygen as is requisite, or else the normal supply is so far in excess of the actual demands that the oxygen tension may be appreciably diminished without resultant harm to the organism. In view of what is known of other relations in the animal body, it seems more probable that the second postulate is nearer the fact and we have here another example of what Meltzer has aptly styled "factors of safety." In the erythrocytosis is to be seen a physiologic response to a lowered oxygen tension, having for its end more than an adequate oxygen supply.

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4. Total sulphur determined by method of Benedict (*Jour. Biol. Chem.*, 1909, vi, 363), sulphates by Folin's method.

5. A patient from the surgical division of the children's ward of the New York Hospital was used as a control. He had been admitted to the hospital for a slight operation from which he had recovered so far as to be out of bed and about the ward at the time the specimens of urine were collected. Although the "control" was of about the same age as the subject of this report, he was larger, heavier, and ate more. The total nitrogen averaged 6.45 gm. daily and the sulphur was correspondingly increased over the amounts indicated in the first part of the table.

6. Benedict, H.; *Ztschr. f. klin. Med.*, 1899 xxxvi, 281.

## ADIPOSIS AND LIPOMATOSIS

CONSIDERED IN REFERENCE TO THEIR CONSTITUTIONAL RELATIONS AND  
SYMPTOMATOLOGY \*

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### *Synopsis*

Introduction. Personal observations (20 cases, 19 photographs). Consideration of special clinical varieties or syndromes—groups of cases. Group I. Adiposis dolorosa. Group II. Obesity. Group III. Nodular circumscribed lipomatosis. Group IV. Diffuse symmetrical lipomatosis (*Fetthals*, Madelung; *adipo-lipomatose symétrique à prédominance cervicale*, Laureis and Bensaude). Group V. Neuropathic edema, pseudo-edema, pseudolipoma and lipoma. Group VI. Adipositas cerebri (Fröhlich, Madelung and others). Consideration of the combined groups. General summary (including special subjects, arthritism, heredity, etc.). Etiology (including glands of internal secretion). Treatment. Conclusions. Bibliography.

### INTRODUCTION

The object of this study is to simplify or unify the clinical classification of abnormal subcutaneous fat deposits by correlating the symptomatology and constitutional relations common to the several varieties or clinical groups that have been separated under descriptive designations according to their predominant characteristics. It is with special reference to Dercum's "adiposis dolorosa" that this study is undertaken. I shall present in evidence a series of personal observations and then proceed to take up in order the different clinical varieties of abnormal fat deposit, showing the blending of these several varieties by their common features and emphasizing the constitutional relations and symptomatology of the process in general.

### PERSONAL OBSERVATION

CASE I. *Summary*.—Typical case of Dercum's syndrome, elephantiac form. Woman, 61; family history of insanity; enormous diffuse adiposity limited to legs, thighs and hips; marked tenderness; asthenia; deafness; rheumatoid pains; insanity; suicide.

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\* Presented in abstract before the Association of American Physicians, twenty-fourth annual meeting, Washington, May 11, 1909.



Fig. 1.—Patient 2: typical Dereum's syndrome.

*Patient.*—Mrs. L., aged 61, born in United States, widow, no children, no miscarriages, admitted to the Buffalo State Hospital (Hospital No. 11157) Jan. 23, 1909, discharged July 11, 1909; diagnosis: acute toxic-exhaustive insanity, adiposis dolorosa, chronic bronchitis, chronic nephritis.

*Family History.*—Mother said to have been insane and to have attempted suicide; otherwise negative.

*Personal History.* Usual weight is 215 pounds. In consequence of obesity and asthenia the patient has been compelled to lead a very inactive life. No statement of the duration of the adiposity, pain and asthenia. History of rheumatoid pains in fingers and legs (not in joints), which her "physician did not regard as rheumatism." Deafness in both ears has been developing gradually for six years; pneumonia in November, 1908, followed by mental depression and insanity with attempted suicide, requiring her commitment in January, 1909.

*Physical Examination.*—(Made on admission to the Buffalo State Hospital, Jan. 23, 1909.) "Excess of fat especially in the lower limbs, which are monstrously enlarged, and where the rolls of fat are very sensitive to the touch (adiposis dolorosa); below the knees are many varicose veins." Skin everywhere soft and normal; no edema. Terminal joints of the fingers thickened. Vision imperfect; patient wears glasses; no hemianopsia. Hearing very defective; watch cannot be heard on contact with either ear. Knee-jerks active, no ankle-clonus. Dyspnea constant, soft mitral bruit, signs of general bronchitis, systolic blood-pressure 190 mm.; some arteriosclerosis palpable in radicals and visible in temporals. Urinalyses show considerable albumin, granular casts and pus cells.

*Subsequent History.*—An interview with the patient was arranged for me for July 28, 1909; when I called at the house in the afternoon the door-bell was not answered, and later it was found that the patient, who had been left alone at home, had committed suicide by hanging. I examined her body after death the next morning. The excessive fat deposit, diffuse, involved the legs, thighs and hips only, the rest of the body showing only a moderate panniculus adiposus. No other abnormality was apparent. Necropsy refused.

I am indebted to Dr. Arthur W. Hurd, superintendent of the Buffalo State Hospital, for the privilege of reporting this case.

CASE 2.—*Summary.*—Typical case of Dercum's syndrome, elephantiac form (Figs. 1, 2, 3, 4). Woman, 75; history of trauma at 25 followed by mental irritability; asthenia; areas of edema with local soreness; painful adiposity. Marked vasomotor instability; areas of redness and blueness and of swelling with increase of local pain; hemorrhages from the nose and mouth followed by relief of pains; anidrosis; macroglossia. History of symmetrical, painless lipomata in a hysterical daughter.

*Patient.*—Mrs. D. T., aged 75, married; five children; born in United States; height, 5 feet and  $\frac{1}{2}$  inch; weight, 176 pounds; seen in consultation with Dr. Joseph S. Lewis, April 24, 1909.

*Family History.*—Negative, except that father and mother were of the high-strung, nervous type and that a daughter of the patient developed in early childhood two symmetrically-placed, painless lipomata, one on each side of the back in the region of the kidney, about the size of a hen's egg, which remained unchanged and symptomless until her death from typhoid fever at twenty. This daughter also had a paralysis and was unable to walk for several years until she was suddenly cured by a few electrical treatments in a quack medical institution (hysteria).

*Personal History.*—Menses always normal, menopause at 58 without notable symptoms. At 25 the patient fell down stairs, receiving a "concussion of the spine," from which she dates her subsequent trouble. Following this accident she became very irritable and nervous; worried over trifles; suffered pain over the



Fig. 2.—Patient 2: back view.

dorsal spine and grew weak. Soon thereafter she noticed a condition of "bloating" in various parts of the body, especially over the knees and ankles, with soreness in the affected parts, both relieved considerably by rest in bed for a few days. At the same time she gradually put on fat and became stout. The fat has always been more or less tender and painful on pressure and the painfulness has always been increased by work, with spontaneous aching in the legs and arms. The pain has never been referred to the course of any special nerves. After the birth of two of her children, during the puerperium, both legs became greatly swollen and painful, keeping her in bed for five months or longer. Since middle life she has



Fig. 3.—Legs of Patient 2.

suffered more or less constantly with a "poor circulation," manifested by chilly sensations and numbness over the body, especially in the feet and legs. During the past seven years she has noticed after hard work areas of redness and blueness over the fatty deposits with increased soreness in the discolored regions, always relieved by rest. During the past four years she has had frequent hemorrhages from the nose and mouth, sometimes very profuse, invariably followed by relief of pain and soreness over the entire body. Occasional headaches for two years. Small pigmented spots on the skin have developed during the past ten years. For a long time the skin has been dry and has flaked, never sweating even



in summer. The patient does a little light work and supports an invalid husband, but has suffered with some general weakness and ready fatigue since the age of 25.

*Present Condition.*—The distribution of the abnormal fat deposit is so well shown in the accompanying illustrations that no detailed description is necessary. The hands, feet and face are spared and the trunk is not much involved. The legs suggest elephantiasis. The upper arms hang in the form of fat-bags, which on palpation give the feeling of a "bundle of worms." The fat feels irregular or slightly lobulated but nowhere can any distinct lipomas be made out. Firm pressure is everywhere painful, but unequally, being more pronounced in the legs and thighs; hyperesthesia over the dorsal region is apparently increased by the patient's mental excitement and fear of being hurt. The skin is everywhere dry and desquamating in small flakes; numerous small pigmented spots over the arms; veins and venules over the fatty tissue enlarged and over the thighs small varicosities; no varicose ulcerations or scars. The tongue is enlarged, rather "too



Fig. 4.—Arm of Patient 2.

large for the mouth" as the patient remarked, and shows many varicose veins along its margin. Heberden's nodosities on terminal joints of fingers with slight deformity of these joints. Heart shows a soft systolic bruit at the apex, not transmitted; pulse, 70 per minute, regular, tension normal. Marked asthenia is evident. No psychical disturbance beyond some slight nervousness and irritability; the patient is intelligent and answers questions promptly and accurately. No anemia. Urinalysis shows a low specific gravity, a trace of albumin and rare hyaline casts.

*Treatment.*—Tonics and desiccated thyroid were given for three months with no notable improvement; the only change observed was in the skin, which lost its dryness and desquamation with the return of normal sweating.

For the excellent photographs (April 25, 1909) I am indebted to Dr. Grover W. Wende.

CASE 3.—*Summary*.—Dercum's syndrome, generalized diffuse and nodular mixed form (Figs. 5 and 6). Woman, 55, from childhood has always had tender flesh with a tendency to bruising, a peculiarity shared by two daughters; maximum weight 244 pounds, reached at 40; at 45, "double plantar neuritis and hysterical edema" of feet and lower legs; at 47, menopause, followed, at 50, by development of painful lumps in the subcutaneous fat, asthenia and nervousness; occasional appearance of local redness over the lumps with exacerbations of pain; at 55, severe epistaxis, followed by subsidence of lumps and pain.

*Patient*.—Mrs. P. S., aged 55; born in United States, married; nine children; two miscarriages; medium height; weight 235 pounds; admitted to the Buffalo General Hospital April 21, 1909, for severe epistaxis; seen in consultation with Dr. Charles Cary, April 24, 1909; photographed April 30, 1909.

*Family History*.—Antecedents normal. Two daughters, aged 34 and 37 years and weighing 150 and 170 pounds respectively, have from childhood suffered from tenderness of the flesh on slight pressure and from a tendency to ready bruising of the flesh from slight blows, a peculiarity shared by the patient. Both of these daughters have always been nervous; one of them (see Case 4) was epileptic from 3 to 8 years of age; for years has had cramps in her feet, legs and thighs, tender, aching shins, tendency to goose-flesh on excitement, ready flushing of the skin, general nervousness and irritability, and now, on examination, shows fat-bags dependent from both upper arms, considerably painful on pressure. One son, aged 20 years, weighing 170 pounds, for the past four years has had a pronounced tendency to epistaxis, using on the average about five handkerchiefs a week for nose-bleed. He is strong and hearty.

*Personal History*.—From childhood the patient has always suffered from a peculiar tenderness of her flesh, the slightest blow causing pain and a black-and-blue discoloration. Throughout her childhood this vulnerability required her to guard herself against the rough play of other children. This tendency has continued ever since to the present time. At 14, she had an attack of epistaxis, from which she says she almost bled to death. She was married at 17, at which time she weighed 166 pounds, gradually increasing to 200 pounds at 30 and to a maximum of 244 pounds at 40, since which her weight has remained almost stationary. At 45, after arduous work, her legs below the knees and feet became bloated, painful and numb and her gait insecure from a feeling as though her feet were not touching the ground. Dr. William C. Krauss, who treated her at the time informs me that his diagnosis was "double plantar neuritis and hysterical edema." Menses were always normal; abrupt menopause at 47. At about 50, the patient noticed lumps under the skin, at first three between the shoulder-blades on the left side, small, firm, movable and tender on pressure; soon similar lumps were noticed in the forearms, arms and thighs, in all perhaps a dozen, varying in size from a pea to a walnut. These lumps gradually increased in size and tenderness; variations in the degree of tenderness occurred from time to time and spontaneous aching and soreness in the lumps was suffered at times. The use of the arms, as in knitting or kneading bread, sometimes led to the appearance of redness of the skin over the lumps in the arms with paroxysms of pains radiating from the lumps upward into the shoulders, neck and head. Since the development of the lumps, the patient has noticed an increasing degree of fatigue and weakness, feeling tired much of the time, and during the same period she has grown nervous and irritable; at times she has felt peculiar "flashes" run over the body, leaving her excited and restless. At 53, hemorrhage occurred in the left retina, causing permanent loss of sight in that eye. For about two weeks preceding April 20, 1909, the pains in the arms were more severe and constant than ever, on account of which the patient took a sweat bath on the night of April 20. This was followed in a few hours by profuse epistaxis, from which she fainted. The bleeding continued until the next day when she entered the Buffalo General Hospital and received surgical

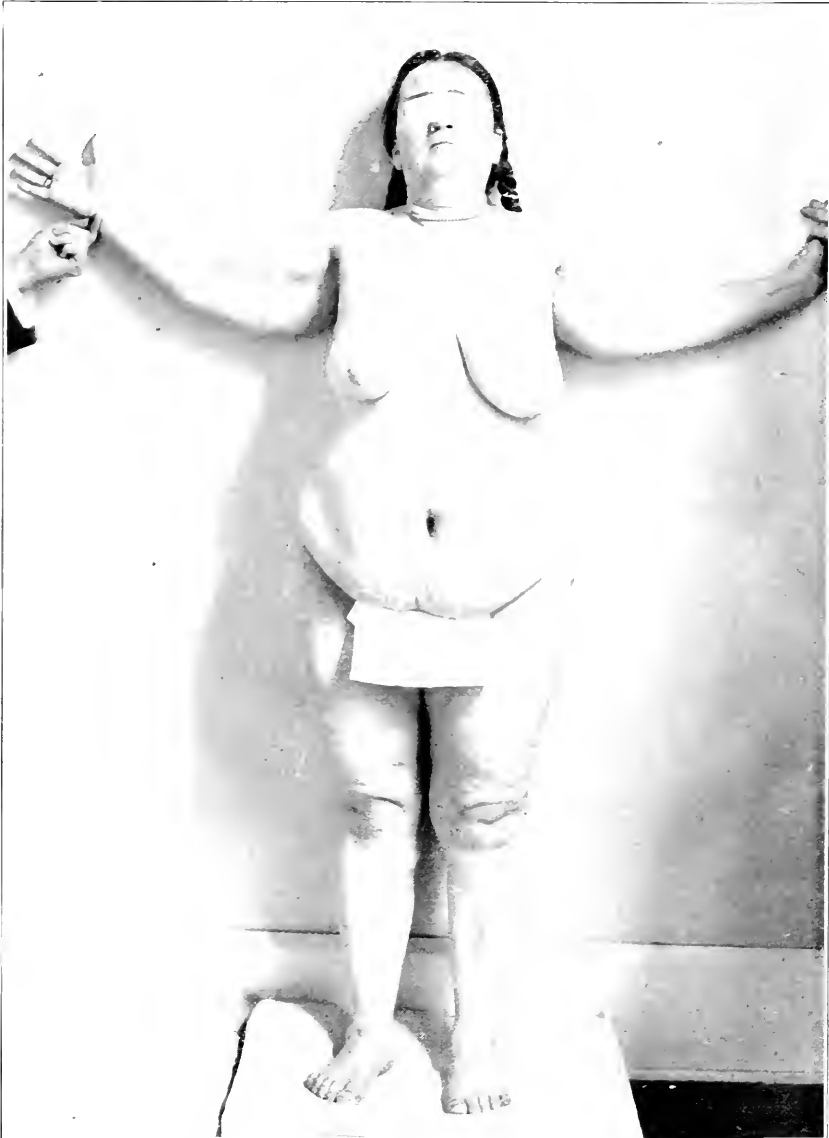


Fig. 5.—Patient 3: Darier's syndrome, generalized diffuse and nodular mixed form.

treatment. Shortly after the loss of blood, the spontaneous pains in the arms, which had been severe and continuous for two weeks, subsided until in two or three days they had completely disappeared. At the same time the several lumps in the skin lessened in size and tenderness until on April 24 some of them could no longer be found and others were very small and only slightly painful on firm pressure.

*Physical Examination.*—(April 30, 1909.) The condition of general obesity is shown in the accompanying illustrations. The face, hands and feet are spared. The fat is everywhere sensitive to slight pressure and firm pressure causes marked pain. The larger deposits of fat feel irregular and finely lobulated. In the fore-arms, arms and thighs several small, firm, movable nodules can be felt embedded in the general fat tissue and at their margins apparently fusing with the surrounding fat. The skin is everywhere soft, moist and normal in texture. General reflexes normal; sensations of the skin normal; hearing, taste and smell normal. Muscular power deficient. Mentality perfectly clear. Thyroid seems to be small. Heart, lungs, abdominal organs, normal; blood-pressure not increased. Urinalyses show a high specific gravity, slight trace of albumin and occasional granular casts. Blood examination (April 24): hemoglobin, 65 per cent.; red corpuscles, 3,100,000; leucocytes, 10,000, differential leucocyte count, normal.

*Treatment.*—Thyroid medication was begun on April 27 but was interrupted by the departure of the patient from the hospital very soon thereafter.

*Subsequent Condition.*—On Aug. 7, 1909, the patient wrote: "Those fatty lumps have continued to be reduced in size and I think that they are gradually disappearing. They have caused me no pain since my severe nosebleed."

*CASE 4.—Summary.*—Atypical case of Dercum's syndrome, hereditary (Fig. 7). Woman, 34, no unusual fat deposits except moderate fat-bags in upper arms; abnormal tenderness of flesh and marked tendency to bruising of flesh from childhood, a peculiarity shared equally by mother and sister; no asthenia; nervous and excitable; subject to cramps in legs and feet; epilepsy in childhood. Mother (see Case 3) has Dercum's syndrome now in typical generalized, diffuse and nodular mixed form; a sister has a condition similar to her own; mother and a brother subject to unusual epistaxis.

*Patient.*—Mrs. J. J. M., aged 34; born in United States; married; one child; medium height; weight 150 pounds; seen April 24 1909; photographed April 30, 1909.

*Family History.*—See above, Case 3.

*Personal History.*—From three to eight years of age, the patient had frequent epileptic seizures with loss of consciousness, none since. From childhood she has always had tender flesh so that slight blows or pressure were painful and caused black-and-blue marks, requiring her to protect herself against blows. This tenderness was general but more pronounced over the lower legs and the fleshy pendulous upper arms. Walking often causes her shins and legs to feel sore and to ache, so that she has to rest. She has always been subject to severe cramps in the feet, legs and thighs, coming on while at rest in bed, while sitting quietly, or when exercising. These cramps sometimes cause her feet to be jerked off the floor. She has always been nervous and excitable, frequently flushes and has a marked tendency to "goose-flesh" when excited. She has always been strong and tireless. The menses have always been irregular in time and amount of flow. She was married at 24 and has had one child; no miscarriages.

*Physical Examination.*—(April 30, 1909.) The patient is plump, not obese, weighing 150 pounds. The flesh feels normal except in both upper arms, where it hangs in moderate-sized "bags of fat," as she describes them. These dependent fatty masses feel slightly irregular, granular and flabby. Pressure on these masses is painful and similarly slight pressure over the shins and legs causes con-



Fig. 6.—Patient 3: back view.

siderable pain; elsewhere the flesh is abnormally tender but not in the same degree as over the legs and upper arms. The patient's mentality seems normal except for a certain degree of nervousness. The thyroid gland is slightly enlarged. The physical examination otherwise shows nothing abnormal.

*CASE 5.—Summary.*—Atypical case of Dercum's syndrome, localized diffuse and nodular mixed form. Woman, 64, marked family and personal history of arthritism; personal history of epistaxis, neuritis, cerebral attacks; tenderness and bruising of the flesh from childhood, a peculiarity shared equally by three sisters and one daughter; during the past five years development of subcutaneous fatty lumps, painful spontaneously and on pressure, and during the same period, loss of strength; during the past year increased adiposity over abdomen and hips. Mentality normal. A similar condition in a cousin.

*Patient.*—Mrs. H., aged 64, born in United States, widow, three children, no mis-carriages, about 5 feet in height, weight 163 pounds, seen in consultation with Dr. Lawrence Hendee several times during the past four years.



Fig. 7.—Patient 4; atypical Dercum's syndrome, hereditary.

*Family History.*—Antecedents normal; no nervous or mental diseases or adiposity. A sister was crippled for forty years by arthritis deformans; another sister has attacks of migraine; a third sister is very stout and is now suffering with a cerebral condition with headaches, vertigo and attacks of vomiting; a brother had attacks of lumbago; a niece has gout; a daughter and a son are subject to neuralgias and another son to lumbago. Like herself, the patient's three sisters and only daughter have always from childhood suffered with a condition of tenderness and bruising of the flesh from slight blows or pressure, requiring them to protect themselves. A cousin, A. R. M., son of her father's brother, aged 51, height 5 feet 8 inches, weight 190 pounds, was examined on Feb. 2, 1910, by Dr. Lawrence Hendee, who has kindly furnished the following notes: Symmetrically placed in the lumbar region just below the location of the kidneys, there is a pair of soft, indistinctly lobulated lipomata, about the size of a half orange, quite painful to pressure. These lumps were first noticed about six years ago and have varied in size and consistency from time to time. They have been always tender

to pressure, constantly painful, and subject to paroxysmal increase of pain corresponding to the periods of increase of size and consistency. With these exacerbations pains radiate from the tumors down the back into the thighs. Another pair of small symmetrical lipomata is found in the dorsal region between the shoulder-blades, readily felt but not seen, embedded in the abundant subcutaneous fat deposit, distinctly painful to pressure. For the past few years the flesh has been growing flabby without any actual increase in weight. The flesh is everywhere slightly but definitely tender on moderate pressure, more than in a normal person. There is a marked history of ready bruising with black-and-blue discoloration from trifling causes; several attacks of cervicobrachial neuralgia; very ready sweating; headaches; mentality somewhat neurasthenic of late. Patient has had "heart trouble;" no asthenia, arthritis, hemorrhages, or edema.

*Personal History.*—Tenderness and tendency to bruising of the flesh from slight blows or pressure have been present from childhood (see above, Family History). From 15 to 35, patient had attacks of severe exhaustion after any hard work. Menstruation began at 13, was usually painful, ceased abruptly at 44; patient had three children, no miscarriages. At 27, three days after birth of her second child, she had convulsions for three days and inflammation of the right eye, since which vision has been blurred (one-fifth normal vision). At 32, one year after the birth of her last child, she had repeated epistaxis, exhaustion and headaches, continuing for about a year. At 33, after a period of menorrhagia, she had two chills with fever followed at once by a condition of delirium and semicoma; this lasted about six weeks and was followed for a period of a year by difficulty in maintaining the balance on standing. At 54, after a severe mental shock, she had an attack of semicoma alternating with delirium lasting four days and severe headache lasting about two weeks longer; at 56, slight attack of sciatica, left side; at 60, left cervicobrachial neuralgia or neuritis with torticollis, double episcleritis, dead and waxy fingers in left hand, lasting about a year. Swelling in the left supraclavicular region was noticed at this time. With the same illness, she had also marked cerebral symptoms consisting of vertigo, in which things seemed always to revolve in the same direction, faintness, headaches and vomiting. I saw her at this time and considered the possibility of cerebral tumor. All of these symptoms gradually disappeared in the course of one year. At 62, there was slight effusion in both knee-joints, without local pain, redness, or fever; at the same time there was marked pain and tenderness in both lower legs, apparently following the course of certain nerves. The patient has never had inflammatory rheumatism. For several years Heberden's nodosities have been developing in the terminal joints of the fingers. About five years ago she first noticed some small lumps on the back, which were painful on pressure and became more so with time; similar lumps appeared later at other points. They all tended to increase somewhat in size; none ever disappeared or fluctuated in size more than slightly. Spontaneous pains and soreness are felt in and near these lumps at times. The pains and tenderness are increased by exercise, fatigue or emotional excitement. Since the appearance of these lumps there have been noticed some loss of strength, not very marked, and easily induced fatigue. During the past year her weight has increased from 147 to 163 pounds, the increase of flesh being limited almost exclusively to the region of the abdomen and hips.

*Physical Examination.*—(May 2, 1909.) A somewhat stout woman, whose trunk, arms and legs are well proportioned, with a pendulous abdomen from excessive fat deposit and marked fatty deposits over the hips and buttocks. The entire body is somewhat tender on pressure but this feature is not very pronounced. Embedded in the subcutaneous fat of the back four firm lumps can be readily felt, symmetrically placed on the right and left sides below the ribs. Four similar lumps are found, two between the shoulder-blades, one on the back of the neck on the left side, and one on the flexor aspect of the left forearm. These lumps vary

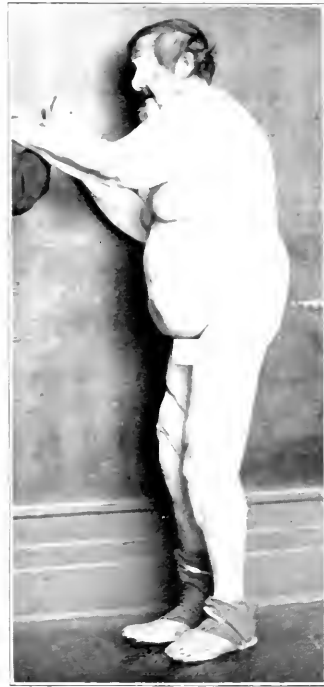


Fig. 8.—Patient 6; atypical Dercum's syndrome, generalized diffuse form.



from the size of an almond to that of a small walnut, are firm, somewhat flattened, indistinctly lobulated, movable, and are not well defined from the surrounding fatty tissue with which they seem to fuse. They are all painful on pressure and manipulation, but in varying degrees. The overlying skin is freely movable. Small Heberden's nodes on the terminal joints of the fingers. Slight creaking in the knee-joints on manipulation, without pain. Slight varicosities over both legs and thighs. No gouty deposits anywhere. Reflexes and sensibility of the skin normal. Heart, lungs and abdominal viscera negative. The radial arteries are not markedly sclerosed; blood-pressure normal. The thyroid gland shows no appreciable change. Urinalyses show no noteworthy changes. Mentality normal.

CASE 6.—*Summary*.—Atypical case of Dercum's syndrome, generalized diffuse form, in a man, developing with senility (Figs. 8, 9, 10); late appearance of



Figs. 9 and 10.—Patient 6, back and side views.

tenderness occurring with marked loss of flesh, later complete disappearance of tenderness, and still later temporary reappearance of painfulness of flesh locally; marked asthenia; senile mentality; sudden on-set of paralysis of lower extremities.

*Patient*.—Mr. H. G., aged 82; born in England; widower; several children; medium height; weight 155 pounds; seen in the service of Dr. Charles Cary, Buffalo General Hospital (Hospital No. 57,343), December, 1908.

*Family History*.—Negative for adiposity or nervous diseases.

*Personal History*.—Fracture of shoulder in early life. At 30, the patient had a fall and was in hospital for six weeks. At 40 he broke the right femur in two places, with no permanent disability. At 48 he had "nervous prostration," was

"numb all over," "shook a great deal," and was weak in his legs; also at this time he developed a chronic varicose ulcer on the right leg. He has had muscular "rheumatism" off and on for many years; never has had inflammatory rheumatism. For several years he has had a small epithelioma on the nose, which has not increased in size materially. At 55 he noticed a marked increase of weight which gradually continued until he weighed 230 pounds. During the past few years his general strength has failed and he has had spells of weakness in his legs with a tendency to fall; during the same time his mental faculties have gradually become enfeebled and his hearing has become impaired on the left side. For the past two years he has complained a great deal of "sore flesh" over the entire body so that he has cried out with pain when his grandchildren have touched him carelessly, and during the same period he has lost greatly in weight so that his clothes no longer fit him. In June, 1908, he was suddenly seized at table with severe pain in the back and abdomen and found himself unable to walk. The pain disappeared in the course of two weeks but the paralysis persisted, on account of which he entered the Buffalo General Hospital, July 23, 1908.

*Physical Examination.*—(December, 1908.) The general adiposity is shown in the accompanying illustrations, the photographs for which were taken in December, 1908, by Dr. Grover W. Wende. The weight is 155 pounds; skin loose and wrinkled, giving evidence of marked loss of flesh; panniculus thick, irregular, pultaceous, flabby, hanging in folds on the upper arms, abdomen and thighs; scar and pigmentation of healed varicose ulcer on right leg and scar from old fracture on front of right thigh; slight varicosities over both legs; no edema; small epithelioma (diagnosis by Dr. Grover W. Wende) on the nose; complexion pallid. The fatty tissue everywhere is excessively painful to pressure or manipulation. Pressure over the larger nerves is no more painful than elsewhere. Pain is complained of in the back and lumbar region, especially on the left side, and dull pain in the left ankle is mentioned. There is evidence of marked general asthenia; the grip of the left hand is weaker than the right; paralysis of both lower extremities, confining the patient to bed. Mentality is clear but senile. Knee-jerks absent, no ankle-clonus, Babinski reflex absent, no spasticity, tactile and thermal sensations intact. Pupils unequal, the right larger than the left, react to light and accommodation; cataract in the left eye. Taste and smell normal. Hearing deficient in the left ear. Thyroid gland feels small. Heart, lungs and abdominal organs negative. Radial arteries somewhat sclerosed, blood-pressure normal. Urinalyses show a trace of albumin and a few granular casts.

*Subsequent Course.*—The patient left the Buffalo General Hospital and entered the New York State Soldiers' and Sailors' Home at Bath, New York, on Dec. 10, 1908, where he has since remained. I am indebted to Dr. Clayton K. Haskell, surgeon in charge, for the following notes on his condition:

April 28, 1909: "Since admission here the pain on pressure over the fatty deposits has disappeared, his weight has remained stationary (155 pounds) and no change is noticeable in the growth on the nose. He is at present fairly comfortable, spends most of every day in a chair, eats and sleeps well and is apparently contented and happy."

August 3, 1909: "Mr. G.'s condition since my last letter has been practically unchanged with one exception. Early in July he complained of vague indefinite pain and on examination the areas over the fatty deposits just below the gluteal folds were markedly tender on pressure. This tenderness disappeared in a day or two and since then has not recurred. The growth on the nose (which, by the way, we think is lupus) remains the same as when admitted in December of last year. I have just had him weighed and am informed that he now weighs 174 against 155 pounds four months ago."

Feb. 15, 1910: "Mr. G. remains practically the same as when I last wrote you. The fatty deposits are slightly tender on pressure. The absence of senile

changes generally is striking in this man. No arteriosclerosis, low arterial tension, little whitening of hair, memory for events of immediate past unimpaired, no thickening or harshness of the skin, nails of hands and feet those of a young man, no arcus senilis; in fact, with the exception of his cataracts and slightly impaired hearing there are none of the evidences of senility to be seen in the average man of 84."

*CASE 7.—Summary.*—Case presenting three of the four cardinal symptoms of Dercum's syndrome—no tenderness; elephantiac form (Fig. 11). Woman, 69; diffuse adiposity involving chiefly the legs; absolutely no tenderness; moderate asthenia; insanity; rheumatoid pains and cramps; development after menopause.

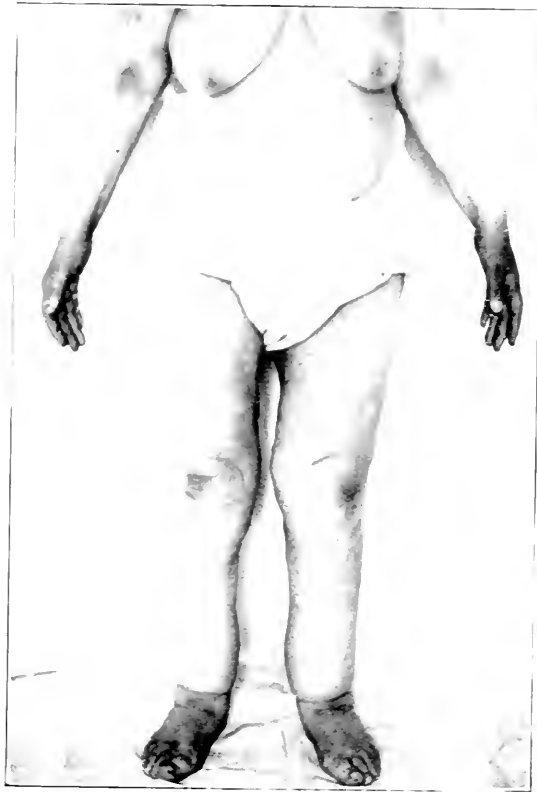


Fig. 11.—Patient 7, presenting three of the four cardinal symptoms of Dercum's syndrome, elephantiac form.

*Patient.*—Mrs. McC., aged 69; born in Ireland; height 5 feet; widow; two children; two miscarriages; admitted to the Buffalo State Hospital, 1898 (Hospital No. 6400,) still confined. Diagnosis: dementia, adiposity.

*Family History.*—Negative.

*Personal History.*—Menopause at 42, followed in about two years by beginning adiposity involving especially the lower legs; weight before menopause, 149 pounds; weight at 59 years 213 pounds. The flesh has never been painful or ten-

der on pressure. The hospital history contains notes on several occasions of rheumatoid pains of a dull, aching character in the knees, thighs, hands and arms; also slight "cramps" in the thighs have been complained of at times; occasional severe headaches for many years; no swelling of joints or signs of arthritis. General weakness, varying in degree, usually slight, since the development of the adiposity. Mentality has been impaired for at least eleven years; the patient was committed for acute mania in 1898, since which she has become rather dull and stupid. No history of hemorrhages; perspiration has always been normal. The hospital record contains the following note: "The legs at first sight suggest elephantiasis, but on closer examination little support for this idea is obtainable." Patient denies ever having had milk-leg.

*Present Condition.*—On July 22, 1909, when I examined the patient, her condition was as follows: The adiposity involved chiefly the legs, to a less degree the thighs, and only slightly the abdomen; fat-bags in the upper arms, hanging like a pouch when the arms were lifted, and on palpation feeling like a "bundle of worms" (Dercum); the abnormal fat was everywhere somewhat irregular, lobulated or slightly lumpy, without distinct separate lipomas. Firm pressure elicited no evidence of pain or tenderness. The skin was soft, flabby and wrinkled, apparently from loss of flesh; occasional small pigmented patches over the skin, especially of the arms; considerable capillary dilatation with resulting blueness of the skin over the abnormal fat deposits, especially in the lower legs; no varicose ulcerations or scars; no edema; double flat-foot. Moderate asthenia. Thyroid felt small. Heart showed no significant changes. Radial arteries not specially thickened, pulse pressure felt normal. The eyes showed slight nystagmus; sight good. Urinalyses, negative.

For permission to report this case I am indebted to Dr. Arthur W. Hurd, for the illustration, to Dr. John L. Eckel and Mr. Dustin.

*CASE 8.—Summary.*—Atypical case suggesting Dercum's syndrome *without adiposity*. Woman, 34; no abnormal adiposity; for ten years diffuse tenderness and soreness of flesh, gradually increasing; also spontaneous, more or less constant, dull aching pains throughout both arms and legs, especially on the left side; paroxysms of general pains and cramp-like pains in various parts of body; accompanying fatigue and moderate asthenia; nervous mentality; hemorrhagic chorioiditis; herpes zoster.

*Patient.*—Mrs. N. A. M., aged 34, born in United States; married; no children; no miscarriages; medium height; weight 146 pounds; referred by Dr. Grover W. Wende, Dec. 31, 1908, for complaint of pains.

*Family History.*—Mother is obese and "rheumatic."

*Personal History.*—The patient has had several attacks of tonsillitis; never had inflammatory rheumatism or swollen joints; double hemorrhagic chorioiditis at 20; herpes zoster in the right lumbar region at 32; menses began at 11, have always been scanty and irregular; no children, no miscarriages. About ten years ago the patient began to have aching pains all over the body and the flesh became sore and painful on pressure; the aching pains were more marked in the legs and arms and especially on the left side. The general soreness and aching at times became more acute and cramp-like pains were felt in different parts of the body. Extreme heat and cold aggravate the pains and depress the patient's vitality; requiring her to go south or north according to the weather. The pains have tended to grow worse since they started about ten years ago. During the same time she has grown nervous and irritable and has lost strength so that she tires easily.

*Physical Examination.*—A plump woman with well-developed panniculus adiposus, not obese, and with no localized deposits of fat. The flesh is everywhere abnormally painful to pressure, not more so over the course of the larger nerves

than elsewhere: the breasts are specially sensitive. Her mentality is neurasthenic; muscular power somewhat deficient. Heart normal; radial arteries not thickened; pulse-pressure normal; blood examination negative. Abdominal organs negative. Thyroid gland not appreciably changed. Tonsils enlarged. No edema. General reflexes and pupillary reflexes normal. Romberg's sign absent, eye examination negative, no evidence of luetic taint. Urinalysis shows indicanuria and oxaluria. Permission to photograph refused.

CASE 9.—*Summary*.—Atypical case suggesting Dercum's syndrome. Woman, aged 72, moderate obesity, moderate tenderness of fat, slight asthenia, normal mentality, chronic arthritis, attacks of sciatica. Distinct improvement of all symptoms from thyroid medication.



Fig. 12.—Patient 10: typical "fatneck" or symmetrical diffuse lipomatosis of the neck.

*Patient*.—Mrs. G., aged 72, born in United States, widow, several children, medium height, weight 180 pounds, seen in consultation with Dr. Frederick J. Parmenter, Dec. 7, 1909.

*Family History*.—Negative, except that mother had "deformed finger-joints."

*Personal History*.—Menses always normal; menopause at 50, without marked sequelae. From the age of 35 she gradually grew stout, the weight reaching a maximum of 180 pounds at about 60, since when it has not increased. From the

age of 35 the subcutaneous fat has been more or less distinctly tender to pressure, never in a marked degree and no more so now than after the first appearance of this peculiarity. During the past ten years the patient has suffered on several occasions from pain and swelling of the ankle and knee joints, without fever, and from chronic pain and stiffness in these joints, resulting in considerable incapacity in walking. During the past ten years there have been also several mild attacks of sciatica.

*Present Condition.*—The patient is moderately obese, and everywhere the flesh is abnormally sensitive to pressure, especially in the thighs and legs, but this tenderness is nowhere excessive. Perspiration and the texture of the skin are normal. The thyroid gland is doubtfully palpable. Manipulation of the knee-joints causes pain and there is some swelling about them. Asthenia is evident, but not more than could be explained by the incapacity produced by the chronic arthritis. The mentality is normal.

*Postscript.*—Desiccated thyroid in small doses was taken from Dec. 8, 1909, to the present time, Jan. 28, 1910. The articular pain and swelling began to lessen soon after the treatment was begun, and the improvement has been progressive. At present there is no swelling and only slight pain and stiffness in the affected joints. There have occurred some loss of weight and lessening of tenderness in the fatty tissue. Dr. Parmenter states that the patient's condition is greatly improved in all respects.

*CASE 10.—Summary.*—Typical case of "fatneck" or symmetrical diffuse lipomatosis of the neck (Fig. 12): symptomless except for chronic "rheumatism" and sciatica dating from the beginning of the fatneck; operation attempted and abandoned.

*Patient.*—Mr. H., born in Germany; married; several children; short, not obese; photographed in 1893; died in 1902, aged 71 years.

*Family History.*—Negative.

*Personal History.*—When a boy the patient fell into a well and was dragged out by his hair, to which he attributed the subsequent development of fatneck. He drank beer freely, as was the custom among Germans. At the age of 40, symmetrical fatty masses appeared behind the ears and gradually extended until they finally encircled the entire neck in a huge collar of fat, presenting in front beneath the chin as a large unsightly mass and extending downward behind so as to form a hump over the upper part of the back at the base of the neck. The growth was gradual and uninterrupted from its first appearance at forty to the time of death at seventy-one. There were never any sudden fluctuations in its size and it was never painful nor tender. Its removal was undertaken in 1888 by Dr. Ernest Wende but was abandoned because of its diffuse character. There were no other fatty masses on the body. The patient was short and thick-set but not obese, though the immense projection from the neck and the low stature gave the impression of a rather stout man. From the age of 40, when the fatneck first began, he was subject to "rheumatism" and sciatica and during the rest of his life suffered much from frequent attacks of pain and swelling in his feet and ankles and of pain in both sciatic nerves. With these attacks he never had fever. Otherwise he was a strong well man, never asthenic or nervous. He died at 71 years of age with edema of the lungs.

The history and photograph are furnished by Dr. Grover W. Wende and members of the patient's family. He was known to me only as a familiar example of street pathology.

*CASE 11.—Summary.*—Symmetrical diffuse lipomatosis; type "fatneck" (Figs. 13, 14, 15): unusual distribution; tenderness; asthenia; deficient mentality; chronic sciatica; "rheumatism;" hemorrhages; anidrosis; dysmenorrhea. His-

tory of same condition in two of patient's sisters, beginning in all at the same time, at puberty, and reaching full development before maturity: one of these sisters insane; one brother and one sister have chronic "rheumatism;" one brother has chronic sciatica, and one brother is obese.

*Patient.*—Miss A. D., aged 33; born in United States of Irish parentage; height 5 feet 2 inches; weight 130 pounds; was admitted to the Buffalo General Hospital (Hospital No. 43,473) June 13, 1903, in the service of Dr. Henry R. Hopkins, complaining of "rheumatism;" photographed Aug. 1, 1903.

*Family History.*—The patient's father is alcoholic; her mother is somewhat nervous; both strong and well. One brother has been crippled with chronic "rheumatism" for thirty years; one sister has had chronic "rheumatism" in the knees for seven years; another brother has had frequent attacks of sciatica on both sides for ten years; and another brother is obese. Another sister, who died in childhood at 31, had a fatty mass in the throat nearly as large as that of the patient, large masses behind the ears, smaller masses in the parotid regions, a large roll of fat over each shoulder, and a large hump between the shoulders. Another sister, aged 26, has a similar fatty mass in the throat, about half the size of that of the patient, also moderate fatty deposits over both shoulders and also in the upper arms. This sister has had delusions and melancholia for three years. In both of these sisters, as in herself, these fatty masses first appeared at puberty, with or just after the establishment of the menses, and reached their full growth before maturity, at the age of about 18 to 20. Neither sister has been asthenic, alcoholic, has ever suffered pain or tenderness in the fatty masses, or noticed fluctuations in the size of the masses.

*Personal History.*—The menses began at 14, were at first irregular, scanty and painful; for the past ten years have been regular, scanty and painful. The fatty masses made their first appearance at 15, gradually grew, reached their maximum size at about 20, and since then have tended to diminish somewhat. They have never fluctuated in size. They appeared simultaneously in the different locations. During their active growth she "felt tired and dead all the time." Since about one year after the masses first appeared she has always been subject to frequent attacks of sciatica, occurring at intervals varying from one week to three months. Damp weather, getting the feet wet, hard work and fatigue seem to predispose to these attacks. For the past three months she has had "rheumatism" in her knees, legs and ankles, with pain and swelling of the joints, slight fever at the onset, and painful lumps in the skin near the knees. She has been moderately asthenic since the fatty masses first appeared, easily tiring and able to do only light work. At school as a child she was dull and always behind other children of her own age in her studies. For years she has been subject to frequent epistaxis and bleeding from the gums. She does not sweat even in hot weather. She has dyspnea on slight exertion. The fatty deposits have never ached or pained spontaneously but have always been somewhat tender on pressure. She says that this sensitiveness in the fatty masses has been such that she could never stand the pressure of any one leaning on her shoulders. She has never taken alcohol in any form and denies all symptoms of syphilis.

*Physical Examination.*—The photographs make a detailed description of the fatty masses superfluous. The circumference of the neck over the mass is  $21\frac{1}{2}$  inches. The dependent breasts measure 8 inches in their vertical diameter. The symmetrical folds covering the back measure vertically from above downward 5, 6 and 4 inches respectively. The consistency of the masses surrounding the neck varies from semicystic behind the ears to rather firm in the dependent portion in front. Embedded in the mass in front, two firm, discrete, hickory-nut-sized, movable nodules can be felt, one in the median line an inch below the chin, the other just to the right of this. The overlying skin is not adherent except in front







Fig. 14.—Patient 11; side view, showing unusual distribution of fatty masses.



Fig. 15.—Patient 11: back view.

over the dependent portion. The breasts in their lower portion feel rather firm. The hump between the shoulders is soft and elastic. The folds on the back are soft and flabby. The skin over them is somewhat adherent. The fat-bags dependent from the upper arms are flabby and feel like a "bundle of worms" (Dercum). There is no pitting on firm pressure anywhere in the several masses. The point of the chin is prominent, caused by an elastic, firm, fatty deposit. The masses are generally tender on moderate pressure, distinctly more so than the rest of the body or than would be expected in a normal person. The general muscular power is deficient. The mentality is clear but deficient and imperfectly developed for a person of her station. The general physical examination, including heart, lungs, abdominal organs, reflexes, sensations, organs of special sense, etc., reveals no abnormality. The thyroid gland cannot be felt.

*Treatment.*—Thyroid was administered for more than two months without any apparent benefit or effect on the fatty masses.

*Subsequent History.*—Writing May 19, 1909, almost six years since I saw her, the patient said: "Well, I can't see as there is any change in the lumps, but other ways I feel pretty well; my rheumatics bothers me some but I am not lame. My sister is dead." The sister referred to is the one who was insane and with fatty masses.

*CASE 12.—Summary.*—Diffuse symmetrical lipomatosis; slight tenderness; fatigue; no mental symptoms; several attacks of neuralgia and neuritis.

*Patient.*—Mrs. J. R., aged 40; born in Canada; married; one child; no miscarriages; tall; weight 160 pounds; consulted me June 22, 1906, complaining of "lumps in legs."

*Personal History.*—At 25 neuralgia in right side of neck and back of ear. At 35, pain and soreness of both Achilles tendons, more marked on right side. At 36, neuritis of right arm, lasting two months. Fatty lumps appeared on the inner aspect of both knees ten years ago, on the right hip seven years ago, and below both external malleoli about a year and a half ago. On account of the increase in size of the lumps on the ankles the patient now consults me. These deposits have never pained spontaneously but have been subject to "soreness" on pressure. The patient has always been strong. No history of inflammatory rheumatism. She has one child 7 years old; no miscarriages.

*Physical Examination.*—A large well-built woman, with a well-developed panniculus adiposus, not obese. Below each external malleolus there is a soft, diffuse pad of fat, about the size of half a hen's egg. On the inner aspect of the legs, at the knees, similar larger deposits of fat are found, and on the right buttock there is a single diffuse fatty mass about the size of half an orange. These masses are not circumscribed and appear to fuse with the surrounding fat. They are all slightly but definitely painful on pressure. Equal pressure exerted elsewhere over the body is not painful. Muscular power normal, mentality normal.

*Subsequent History.*—The patient consulted me again on June 15, 1907, since which I have not seen her. She was then suffering with an attack of sciatica on the left side, which she had had for a month. The fatty masses were of the same size as a year before but were entirely painless on firm pressure. The only additional information of interest obtained was the statement that she was always tired, wanted to sleep all the time, never waked refreshed and was not as strong as she used to be.

*CASE 13.—Summary.*—Multiple encapsulated lipomata, symptomless.

*Patient.*—L. M. W., aged 30; born in United States; single; a medical student; height 5 feet 10 inches; weight 160 pounds; was referred to me by Dr. Grover W. Wende, April 26, 1909. He was a strong healthy young man, without nervousness, with a good family history, whose only complaint was the develop-

ment during the past two years of small lipomas in the left forearm and left thigh. They had never been painful, could be firmly pressed with impunity, and were increasing in size and number. They were firm, discrete, lobulated, varying in size from a pea to a cherry, situated as follows: four on the flexor surface of the left forearm, radial side, arranged longitudinally over a distance of six inches, one on the back of the left forearm on the radial side and one on the front of the left thigh. No history of rheumatism, neuralgia, neuritis, or other symptoms.

*CASE 14.—Summary.*—Solitary lipoma, painless, symptomless except for "rheumatism." Recurrence after complete excision. Son had multiple, partly symmetrical, encapsulated lipomas and is "rheumatic."

*Patient.*—Dr. H. H., aged 52; born in United States; married; several children; height 5 feet 10 inches; weight 200 pounds; had a solitary lipoma, lemon-sized, excised from the posterior inner aspect of the left thigh by Dr. Eugene A. Smith, in 1887. After about three years a similar tumor appeared at the same site and enlarged until it reached its maximum size in 1905. It is now (April 30, 1909), on examination, found to be soft, lobulated, sharply defined, and about the size of a small orange. It is not painful or tender on firm pressure and never has been. The patient is a strong man, with a normal mentality and has had no symptoms except atypical articular "rheumatism," from which he has suffered on several occasions. His son (Case 15) is also "rheumatic" and has multiple, partly symmetrical, painless lipomas.

*CASE 15.—Summary.*—Multiple, partly symmetrical, encapsulated painless lipomas, symptomless, except for "rheumatism." Father has a solitary lipoma.

*Patient.*—H. W. H., aged 26; born in United States; married; one child; height, 5 feet 10 inches, weight 200 pounds; presents lipomas distributed as follows: seven on the front and inner aspect of the right thigh, two on the front of the left thigh, one in the left popliteal space, one on the back of each forearm, and one on the back. They are all firm, encapsulated, lobulated, painless to pressure, and vary in size from a pea to a large walnut. They have never been painful or tender. The patient says that they tend definitely to increase in size when he is quiet and inactive and to diminish in size with hard work. He is strong, has a normal mentality and is not nervous. He had an attack of "rheumatism" (pain) in the right knee two years ago, lasting a few days. The lipomas have been increasing in number and in size for about twelve years. His father (Case 14) has a solitary, painless lipoma and is subject to "rheumatism."

*CASE 16.—Summary.*—Multiple, symmetrical, nodular lipomatosis, hereditary (Fig. 16). Each new growth preceded by local burning pain, followed in a few days by black-and-blue discoloration and then by the appearance of the tumor. No asthenia or mental symptoms. Inflammatory rheumatism, neuralgia, phlebitis of the left saphenous vein. Rheumatic family history.

*Patient.*—H. B. M., aged 49, single; born in Canada; height 6 feet; weight 189 pounds; referred by Dr. Joseph S. Lewis, Sept. 21, 1909.

*Family History.*—His father had the same condition of symmetrical fatty tumors with the same distribution in the forearm. These tumors were symptomless so far as patient knows, as he never heard his father complain about them. He weighed for over thirty years before his death 257 pounds and died at the age of 85. Other members of his father's family were stout. Two brothers and one sister of the patient have had inflammatory rheumatism, the sister several times.

*Personal History.*—The fatty tumors began at the age of 18 in the left forearm and thereafter appeared successively during the next twenty years in the different locations, tending to increase in size even up to the present time. In every instance each new tumor was preceded by burning or stinging local pain lasting a few days and followed by the appearance of a small tumor and a black-and-blue

discoloration over it. This discoloration soon faded and disappeared. Otherwise the tumors have never been painful or tender. He attributes each of the tumors to some kind of preceding traumatism, such as strain from jumping or moving a piano. He had severe inflammatory rheumatism involving many joints at the ages of 14, 16 and 35, and severe neuralgia of the face and neck at the age of 20, lasting two months, and slight attacks on several other occasions. He has noticed varicose veins in the left thigh for a few months and about two months ago had phlebitis of the left saphenous vein, while under the care of Dr. Joseph S. Lewis.

*Present Condition.*—He is a strong, athletic, well-muscled man, of good color and normal mentality. The fatty tumors are distributed somewhat symmetrically in both forearms, arms, thighs and back in lumbar region. They vary in size from a bean to a large hen's egg, forming conspicuous deformities especially on the forearms. They are lobulated, circumscribed, typical lipomata. Firm pressure causes no pain. He perspires normally and has no other symptoms of note. Photographed Feb. 17, 1910.

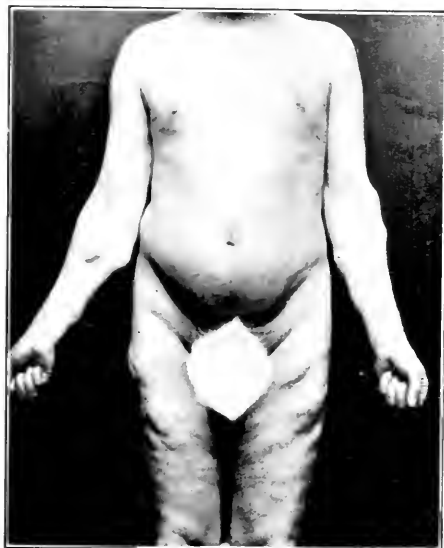


Fig. 16.—Patient 16; multiple symmetrical nodular lipomatosis, hereditary.

*Treatment.*—He was placed on desiccated thyroid from Sept. 21, 1909, to Feb. 17, 1910, with periods of interruption, without any notable effects except a gain in weight from 189 to 202 pounds.

*CASE 17.—Summary.*—Multiple, symmetrical, nodular lipomatosis, painless and symptomless except for "rheumatism" and lumbago (Fig. 17).

*Patient.*—I. A., aged 48, born in United States; married; several children; medium height; weight 160 pounds; seen in the service of Dr. Charles Cary, Buffalo General Hospital (Hospital No. 58,397), to which he was admitted in December, 1908, suffering with lumbago.

*Family History.*—Negative.

*Personal History.*—No history of traumatism; uses beer and whisky usually moderately, sometimes to excess; has always been strong; chancre at 25, without any sequelæ; gonorrhea at 27 and 28; at 17 had "rheumatism" with pain in legs

and arms and stiffness and soreness of joints, without fever or swelling; later had attacks of pain and stiffness in the left shoulder; at 40 had two attacks of lumbago; during the past six weeks has been suffering with lumbago. The fatty tumors began to appear when he was about 10 years old, first in the region of the groins, then over abdomen, chest, arms, legs, etc., multiplying and increasing in size until he was about twenty years old. During the past seven years they have reduced in size considerably and some, the patient thinks, have disappeared. Only once, in his early life, was there ever any pain felt in these tumors, and then only slightly in a single tumor in the abdominal wall when it was first appearing.

*Physical Examination.*—A strongly built, well-muscled, powerful man, with no superfluous panniculus. Numerous, small, subcutaneous lumps are seen and felt widely distributed over the forearms (front and back), arms (back), thorax (front), abdomen (front and sides), and thighs (front and sides). The face, neck, hands, shoulders, upper part of the back, feet and legs below the knees are spared. The distribution of the lumps is strikingly symmetrical. The lumps



Fig. 17.—Patient 17: multiple, symmetrical, nodular lipomatosis.

vary from the size of a small seed to that of a butternut. They are firm, lobulated, somewhat flattened, round or oval, not adherent to the superjacent skin, and freely and equally movable longitudinally and laterally. In some places they appear in chains, corresponding to the course of nerves. They are painless on firm pressure. The photographs were taken April 18, 1909. The thyroid gland feels rather full and firm, but not notably so. A careful general physical examination otherwise reveals no abnormality.

*CASE 18.—Summary.*—Multiple, symmetrical, nodular, painful lipomatosis (Fig. 18); no asthenia; slight nervousness; recurrence after excisions; onset of each new growth announced by preceding local pain, tenderness and blueness. Microscopic examination of smallest tumor shows a small nerve within the growth.

*Patient.*—Mrs. E. M. E., aged 42; born in United States; height 5 feet 8 inches; weight 155 pounds; married; three children; no miscarriages, referred

April 17, 1909, by Dr. Grover W. Wende for painful fatty tumors; photographed April 18, 1909.

*Family History.*—Negative for obesity, tumors, insanity, nervous diseases, alcoholism, etc.

*Personal History.*—Menses began at 15, always normal; three children, no miscarriages; no history of syphilis, alcoholism or rheumatism; occasional headaches; has always been strong, works hard and is not easily fatigued; has always been somewhat nervous, excitable and easily worried. The tumors first appeared in both forearms when the patient was 25, and were all excised three years later by Dr. Grover W. Wende. Within a year new tumors appeared, some directly under the scars of the previous incisions and others at new points, all being located in the forearms except one in the left axilla. When the patient was 35 all the tumors, about fifteen, were again removed by Dr. Wende. The largest tumor was about three inches in diameter and all, according to the statement of Dr. Wende, were typical encapsulated lipomata. Since the second removal new tumors have appeared, as before, in the sites of the excised growths and elsewhere. In every instance the growth of a new tumor has been announced by preceding

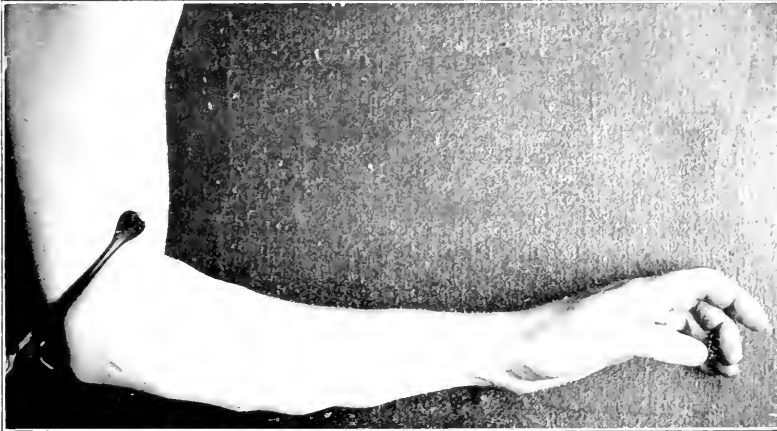


Fig. 18.—Patient 18; multiple, symmetrical, nodular, painful lipomatosis.

local pain. On examination a small blue area, painful to pressure, is found, and within a week or two a small shotty nodule can be felt under the skin. The spontaneous pain usually disappears soon after the nodule is felt but tenderness on pressure continues. The area of blueness sometimes enlarges and remains with the growth of the tumor, sometimes disappears. Spontaneous aching pain in the tumors and shooting pains in the arms are sometimes excited by using the arms as in washing and ironing, but are always relieved by a night's rest. No sudden fluctuation in the size of the tumors has ever been noticed.

*Physical Examination.*—The patient is a tall, sparely built woman, weighing 155 pounds, with a normal panniculus. She has a good color and looks strong and well. Her expression and manner suggest a nervous temperament. The muscular power is normal. Heart, lungs and abdominal organs normal. Radial pulse normal, blood-pressure not increased. Thyroid gland normal. Knee-jerks somewhat exaggerated. Pupils moderately dilated, equal, react to light and accommodation. Fine varicosities on both thighs and legs. A soft, lobulated fibroma molluscum, about an inch and a half long, attached by a narrow peduncle,

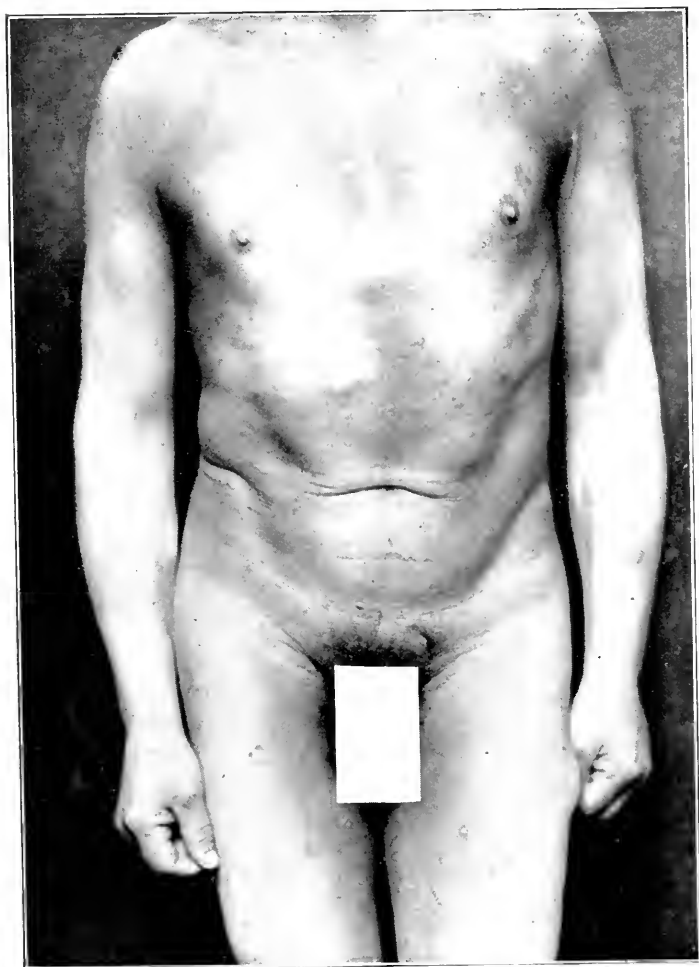


Fig. 19.—Patient 20; multiple, symmetrical, encapsulated lipomatosis.



is found in the right axilla. Urinalysis negative. Fifteen tumors are found located as follows: eight in the left forearm, front and back, four in the right forearm, front and back, two in the right arm just above the elbow, and one in the back of the right thigh, just below the gluteal fold. They vary from the size of a buckshot to a walnut, are round or oval, subcutaneous, not adherent to the skin, freely movable in all directions, circumscribed, firm, slightly lobulated. A few of these tumors are situated exactly beneath small linear scars. The tumors in the forearms are not entirely symmetrical in arrangement and number, but in general a considerable degree of symmetry is clearly indicated. The distribution tends to be longitudinal in the axis of the arms, thereby suggesting a relation to the course of nerves. At a glance the forearms appear nodular or lumpy. The smallest tumors are indicated by a distinct blueness, evidently caused by congestion beneath the skin; a slighter grade of blueness is seen over some of the larger tumors but is entirely absent over the largest lumps. The smallest tumors (blue) are very painful to pressure; the largest tumor is so sensitive that it can hardly be touched without causing pain, although it is entirely free from any blueness; a few of the medium-sized tumors are not at all tender. There is no tenderness in the general subcutaneous fat and the larger nerve-trunks are not sensitive. The smallest tumor that could be found (duration six weeks), distinctly blue in color and tender, was excised from the arm, April 18, 1909, and examined microscopically. It was not larger than the head of a match. It was found to be an encapsulated lobulated lipoma. A small nerve bundle was found in its center within a connective-tissue septum. The axis cylinders stained poorly, were shrunken, and the connective-tissue nuclei were increased in number above what might be expected in so small a nerve bundle, giving the impression of an interstitial neuritis.

*CASE 19.—Summary.*—Painful solitary lipoma, chronic rheumatoid pains. Microscopic examination: no nerve fibers.

*Patient.*—Dr. T., aged 24; height 5 feet 6 inches; weight 158 pounds; born in Canada; seen April 18, 1909.

*Family History.*—Both parents are somewhat stout and father has had chronic "rheumatism."

*Personal History.*—For five years has had rheumatoid pains near the joints, especially the right hip and right shoulder, occurring irregularly in attacks, without swelling, redness or fever. About one year ago some local pain directed his attention to a small subcutaneous nodule located in the right forearm, which has since increased in size. This nodule has always been tender on pressure and in addition at times aching pain has radiated from it through the forearm. A similar nodule may perhaps be developing in the front of the right thigh, indicated by a point of pain and a doubtful induration felt on palpation. He is otherwise in all respects well and normal.

*Examination of the Tumor.*—The nodule in the right forearm was excised by Dr. Grover W. Wende, July 28, 1909. It was about the size of a pea, encapsulated, lobulated, was readily shelled out and had the gross appearance of a simple lipoma. On microscopic examination it was found to be a definite lipoma, invaded by considerable diffuse connective tissue. No nerve elements could be found in the sections.

*CASE 20.—Summary.*—Multiple, symmetrical, encapsulated, painless lipomata (Fig. 19); dementia; asthenia; chronic "rheumatism."

I was invited during the early part of this year (1909) by Dr. Grover W. Wende to see this case but missed the opportunity. The history is furnished by Dr. Wende, briefly as follows: A peddler, about 50 to 60 years of age, was admitted to the

Erie County Hospital for pediculosis, general feebleness and chronic "rheumatism." There was a mild dementia. He was well nourished, not obese, and exhibited multiple, symmetrical, small lipomata in the forearms, back, abdomen and thighs. They were not tender to firm pressure and the patient said they had never troubled him. The general pigmentation is due to pediculosis.

CONSIDERATION OF THE SPECIAL VARIETIES OR CLINICAL GROUPS OF ABNORMAL FAT DEPOSIT

GROUP I: "ADIPOSIS DOLOROSA," DERCUM'S DISEASE

Since Dercum,<sup>43</sup> in 1892, first proposed the name "adiposis dolorosa," this designation has become generally adopted in medical literature, and the syndrome thus named has been widely accepted as representing a new and distinct morbid entity.

The affection is described in the text-books as a well-defined condition presenting characteristics that make its recognition easy. Little or nothing is said of the occurrence of atypical cases suggesting Dercum's syndrome, but varying from its classical form in different respects. After one has encountered several such atypical cases to one that conforms to the picture of the disease as described, one might reasonably be justified in questioning the propriety of raising the syndrome to the position of a true entity. One must either entertain this doubt or take the alternative of being unable to classify the majority of cases under any satisfactory nosological group.

Such a dilemma has confronted me on several occasions, and I have repeatedly seen the diagnosis of adiposis dolorosa in atypical cases both affirmed and denied by equally competent clinicians.

It will be necessary to pass in review a description of adiposis dolorosa before undertaking to correlate with it the various forms of fat deposit associated with constitutional symptoms—the object of this paper.

*Symptomatology.*—The name, "adiposis dolorosa," proposed by Dercum, at once emphasizes the chief characteristics, pain and fat deposit or painful adiposity. To these two chief symptoms Vitaut<sup>192</sup> added two others, asthenia and psychic manifestations, regarding all four as cardinal symptoms. To this view Dercum<sup>45</sup> gave his qualified approval in the following language:

While fatty deposit and pain are the two most prominent symptoms of the disease, marked or even grave asthenia and psychic or general nervous symptoms were so prominent in all the cases which I have myself observed, that I am equally disposed to ascribe great importance to both of these last-mentioned symptoms.

Vitaut's classification has since become the one most generally adopted, as shown in the following outline:

CARDINAL SYMPTOMS

- |   |   |                                   |
|---|---|-----------------------------------|
| 1. <i>Lipomatous tumors</i> .....   | } | nodular (encapsulated).           |
|   |   | diffuse, localized.               |
|   |   | diffuse, generalized.             |
| 2. <i>Pain</i> .....  | } | induced by pressure (tenderness). |
|   |   | spontaneous.                      |
| 3. <i>Asthenia</i> .  |   |                                   |
| 4. <i>Psychic manifestations</i> (perhaps should be regarded as accessory). |   |                                   |

ACCESSORY SYMPTOMS

- |                             |   |            |
|-----------------------------|---|------------|
| 1. <i>Motor</i> .           |   |            |
| 2. <i>Sensory</i> .         |   |            |
| 3. <i>Sympathetic</i> ..... | } |            |
|                             |   | vasomotor. |
|                             |   | secretory. |
|                             |   | trophic.   |

To show the comprehensiveness of this classification, I have collected, incompletely, a list of the symptoms mentioned in the cases reported in the literature, as follows:

*Cardinal Symptoms*.—Fat Deposit: Dercum emphasized the irregularity of distribution of the deposits and mentioned in particular their character in places as nodular, lobulated, resembling the caking of milk-breast, as though filled with a bundle of worms, like a varicocele, etc. These special characteristics, however, have not been constant in the case reports. The deposits of fat include almost every known variety, both in form and distribution. Diffuse deposits may involve a single small area or a portion or the greater extent of one extremity, or may be symmetrical or even almost universal, sparing usually the face, hands and feet. Even these locations have been invaded in rare instances.<sup>157, 179</sup>

On the other hand, the form of the deposit may be strictly nodular and encapsulated, single, multiple or symmetrical. The inclusion of this last-named variety within the embrace of *adiposis dolorosa* was apparently not contemplated by Dercum before the publication of Vitaut's thesis, and considerably enlarges and at the same time weakens the conception of the affection as an entity, as will presently be shown. Mixed forms of diffuse and nodular (encapsulated) deposits, in great variety, have been described.

*Pain*: This may be of two kinds, induced by pressure (i. e., tenderness) and spontaneous. The former, involving the abnormal fat deposit alone, is more or less constant, though varying in intensity in different cases and in the same case from time to time and in different locations. The absence of this symptom in any given case would seem to exclude such a case from the classification of *adiposis dolorosa*, as an entity, a consideration that will be discussed below. The tenderness on pressure is often characterized by exacerbations, associated with and perhaps

dependent on local changes of circulation, i. e., stasis,\* with increased firmness, tension, lobulation and size of the fat deposits and discoloration (redness or blueness) over the affected areas. Sometimes the tenderness is so slight as to be either not mentioned or even actually denied by the patient and discoverable only to the satisfaction of the examiner.

The second type of pain, spontaneous, is less constant and characteristic, exceptionally being entirely absent. Spontaneous pains are of every kind and description, occur often in paroxysms, are described variously as dull, aching, throbbing, burning, tearing, shooting, etc., and are referred commonly to the location of the fat deposits, sometimes to unrelated parts of the body. The very common pains in special nerves (sciatic, lumbar, cervicobrachial, tibial, peroneal, plantar, etc.), described as neuralgic or neuritic, and in joints, tendons and muscles, as arthritic, rheumatic, rheumatoid, cannot be differentiated from other forms of spontaneous pain and belong to the symptomatology of the affection. Rheumatism or neuritis is a very common diagnosis in the early stages. In some instances these pains precede the development of the fat deposit.

*Asthenia:* This, following Vitaut's classification, has generally been regarded as one of the cardinal symptoms in spite of its complete absence in some cases and its frequent insignificance in many more. It varies in degree from weariness, a tired feeling and readily induced fatigue to extreme muscular weakness with prostration. While in many instances it is explainable as secondary to the incapacity produced by fat deposits and pain, in other instances these factors are clearly insufficient to account for it.

*Psychic Manifestations:* While Vitaut placed psychic manifestations among the cardinal symptoms, he admitted that possibly they should be placed among the accessory symptoms. They are lacking more frequently than any of the cardinal symptoms. They include the whole range of mental changes, as follows: Irritability, quarrelsomeness, instability, modification of character, impairment of memory, insomnia, neurasthenia, hysteria, hypochondria, melancholia, hallucinations, delusions, stupor, coma, mania, attempts at suicide, imbecility and dementia.

*Accessory Symptoms.*—*Motor Symptoms:* In addition to asthenia, classed as a cardinal symptom, the motor symptoms include: tremor, twitchings, cramps, torticollis, epilepsy, impairment of locomotion, paralysis, slowness of speech, aphasia, changes of reflexes, i. e., increased, diminished, abolished.

*Sensory Symptoms:* In addition to pain, these include: anesthesia, hyperesthesia, paresthesia, involving the senses of touch, pain, temperature and position.

**Sympathetic Symptoms:** The symptoms arising from disturbances of the sympathetic nervous system are among the most constant and characteristic, embracing the vasomotor, secretory and trophic functions, as follows:

**Vasomotor Symptoms:** These include the widest range of symptoms of vasomotor instability, and are present in some degree and form in most of the cases. They include the following: poor circulation, dermatographia, urticaria, transitory or persistent edema and swellings or lumps, pallor of the skin, flushings and redness, local redness or blueness over the tumors, tendency to bruising of the flesh, varicosities, hemorrhages (epistaxis, hemoptysis, hematemesis, menorrhagia, purpura, bleeding from the tongue, retinal hemorrhage, etc.), icterus, syncope, tachycardia, palpitation, dyspnea, etc.

**Secretory Symptoms:** These are relatively unimportant, including chiefly anidrosis and hyperidrosis.

**Trophic Symptoms:** Besides the fat deposit, the following trophic changes have been described: desquamation, pigmentation, loss of hair, ulcerations, bedsores, blebs and bullae, herpes zoster, scleroderma, macroglossia, anemia, goiter, exophthalmic goiter, muscular atrophy from neuritis, arthropathies and arthritism (including rheumatic or rheumatoid manifestations, arthritis deformans, Heberden's nodosities, etc.), osseous dystrophies.

In addition to the above-named symptoms, arranged according to Vitaut's classification, may be mentioned the following, arranged according to the organs involved:

**Symptoms of the Genital Organs:** Disturbances of menstruation (including irregularity, menorrhagia, amenorrhea, premature menopause), sterility, impotence, anaphrodisia, hypoplasia of the genital organs.

**Symptoms of the Digestive Organs:** Nausea, vomiting, epigastric distress, hyperchlorhydria.

**Symptoms of the Organs of Special Sense:** Eyes: contraction of the visual fields, hemorrhagic retinitis or chorioiditis, choked disc, blindness, exophthalmus, nystagmus, episcleritis. Ears: deafness, tinnitus. Odor and Taste: impairment.

It must not be understood that in the above formidable list of symptoms, all are referable to the pathology of the affection; many are so, others are probably accidental, arising from complications.

## FAMILY HISTORY

A neuropathic predisposition is commonly noted in the family history. Direct heredity<sup>(a)</sup> in the transmission of the affection is denied by nearly all writers. Hammond<sup>80</sup> has reported, as "adiposis dolorosa," the cases of two sisters presenting symmetrical painful lipomata in the arms.

## SEX AND AGE

Females outnumber males about six or seven to one. Middle life, from 45 to 60 years of age, is the period of greatest incidence. At this period the affection has developed with or followed the climacteric in many instances in women. Exceptionally it has begun in childhood, as early as the eleventh and twelfth years (White,<sup>200</sup> Strübing<sup>179</sup>), or in old age as late as the eightieth year, as in Case 6 of this series.

## COURSE

The onset is usually insidious and the development gradual. Exceptions are noted in case reports of rapid development. In many cases the progress is accentuated by exacerbations with increase in the size and consistency of the fat deposits and in the pains. Periods of remission are common. Death finally ensues from asthenia, cardiovascular-renal complications, intercurrent infections, etc.

## TREATMENT

The treatment is chiefly symptomatic, including massage, hydrotherapy, electricity, x-ray, analgesics, sedatives, tonics, etc. In addition to such general agents, a specific therapy has been sought for in thyroid extract on the hypothesis that the affection is in some obscure way connected with perversion of the thyroid function. Thyroid extract has been tried in many of the reported cases, but without the specific effect that was hoped for. Only two instances of cure<sup>137, 151</sup> (b) from its use have been claimed. Improvement in varying degrees has been reported in many cases, indicated by reduction in the fat deposits, relief from the pains, improvement in the mental state and in the general condition. In many instances no appreciable benefit has been noted. No instance of treatment by pituitary extract has come to my attention.

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(a) Chevers<sup>29</sup> case of symmetrical lipomatosis, reported as "adiposis dolorosa," in a man and his father and sister, is properly excluded in this connection as pain and other symptoms were lacking.

(b) Price,<sup>151</sup> in a personal communication, states that Dercum's case mentioned by him was an unpublished case presented by Dercum in a clinical lecture.

## PATHOLOGY

Only nine autopsies have been recorded: three by Dercum,<sup>43, 44</sup> two by Price,<sup>151</sup> and one each by Dercum and McCarthy,<sup>47</sup> Burr,<sup>23</sup> Ballet,<sup>8</sup> and Guillaïn and Alquier.<sup>76</sup> The more important findings were, as follows:

*Subcutaneous Fat.*—In three cases<sup>23, 44, 47</sup> separate encapsulated lipomata embedded in the diffuse fat were noted. In one case<sup>23</sup> the subcutaneous fat was invaded by much fibrous connective tissue. In two cases<sup>23, 47, 122</sup> hemolymph nodes were found; in both in the subcutaneous fat and in one<sup>47</sup> also in the separate lipomata embedded in the general fat. In both of these cases the spleen was more or less cirrhotic.

*Interstitial Neuritis.*—A condition of chronic interstitial neuritis involving the finer nerves of the painful fat deposit was found in five<sup>8, 23, 44, 47, 151</sup> out of six cases in which a special examination was made; not looked for in three cases;<sup>43, 76</sup> not mentioned in one case.<sup>151</sup> Similar changes in the nerves of the underlying muscles were found in one case<sup>21</sup> and "some thickening of the endoneurium" of the radial nerve in one case.<sup>151</sup>

*Thyroid Gland.*—Changes in this gland were found in eight cases; in only one case<sup>47</sup> was the gland perfectly normal by gross and microscopic examination. The principal changes described were: reduction<sup>43, 44</sup> or enlargement<sup>43, 151</sup> in the size of the gland in two cases each, sclerosis in seven cases,<sup>8, 23, 43, 76, 151</sup> compensatory hypertrophy in three cases,<sup>44, 151</sup> colloid degeneration in three cases,<sup>23, 44, 76</sup> calcareous degeneration in three cases,<sup>23, 43</sup> and inflammatory round-cell infiltration in two cases.<sup>23, 151</sup>

*Pituitary Body.*—This was examined microscopically in six cases and changes were found in all except one.<sup>44</sup> which was absolutely normal. The changes found were: adenocarcinoma in one case,<sup>47</sup> glioma in one case,<sup>23</sup> sclerosis and hypertrophy with increase of the eosinophilic and basophilic cells in one case,<sup>76</sup> normal in size but showing microscopic areas of round-cell infiltration in the glandular lobe and invasion of the nervous lobe by glandular cells in two cases.<sup>151</sup>

*Genital Organs.*—Eight of the nine autopsies were in females. In five cases no mention was made of the condition of the genital organs. In two cases<sup>23, 151</sup> the ovaries were sclerotic, and in a third case<sup>43</sup> an ovarian cyst with hydrosalpinx was found. In the only male<sup>47</sup> in the series the testicles were undeveloped and showed no evidence of functional activity; the penis was small and the hair on the pubis was scanty.

*Adrenal Glands.*—In one case<sup>47</sup> "the right suprarenal gland was about twice the normal size; it showed no abnormality on section"; the left gland could not be found in the surrounding fat. In one case<sup>151</sup> mention was made of "no abnormalities, except certain irregularities in staining."

*Hemolymph Glands.*—See above, Subcutaneous Fat.

*Spleen.*—"Telangiectatic angioma" and "slight interstitial hyperplasia" were found in one case<sup>47</sup> and cirrhosis in another case.<sup>23, 122</sup> In these two cases new-formed hemolymph glands were found in the subcutaneous fat, as above stated.

*Kidneys.*—Chronic nephritis was reported in five cases,<sup>43, 44, 151</sup> acute parenchymatous nephritis in two cases,<sup>23, 47</sup> and multiple cysts in one case.<sup>44</sup>

*Liver.*—Fatty infiltration or degeneration was mentioned in six cases,<sup>8, 23, 43, 47, 151</sup> congestion in one case,<sup>151</sup> cirrhosis in two cases.<sup>8, 44</sup>

*Heart.*—Fatty infiltration or degeneration was noted in six cases,<sup>43, 44, 47, 151</sup> hypertrophy in two cases,<sup>43, 151</sup> dilatation in one case,<sup>43</sup> pericardial effusion in one case.<sup>43</sup>

*Lungs.*—Edema in four cases,<sup>23, 43, 44, 151</sup> emphysema in two cases,<sup>43, 151</sup> hypostatic congestion in one case,<sup>151</sup> old pleural adhesions in two cases,<sup>44, 151</sup> pleural effusion in one case.<sup>43</sup>

*Stomach.*—Dilatation in one case,<sup>43</sup> chronic gastritis in one case.<sup>43</sup>

*Brain.*—In addition to the changes in the pituitary body, the following changes were found: unusual pigmentation of the cortical cells in one case,<sup>44</sup> edema of the brain and pia in one case,<sup>43</sup> "anomalous arrangement of the cortical convolutions" in one case,<sup>47</sup> internal hydrocephalus (associated with glioma of the pituitary body) in one case.<sup>23</sup>

*Spinal Cord.*—Slight degeneration of the columns of Goll in one case,<sup>44</sup> considerable dorsal hydromyelia (secondary to internal hydrocephalus) in one case.<sup>23</sup>

#### ETIOLOGY

Of the etiology nothing definite is known. Various hypotheses have been advanced, but all lack the substantial basis of demonstration grounded on a known pathology or on experimental production of the affection.

Dercum<sup>44</sup> suggested: "It is not inconceivable that, as a result of deranged thyroid action, some substance was thrown into the circulation, which at one and the same time prevented the proper oxidation of the hydrocarbons of the food and tissues, and also acted as a cause of neuritis and nerve degeneration."



Vitaut<sup>192</sup> concluded: "The action of the nervous system in the genesis of adiposis dolorosa is absolutely undeniable." "The cause which sets in operation this mechanism is very probably a thyroid intoxication."

Price<sup>151</sup> said: "It seems, therefore, that sufficient attention has not been given the hypophysis, and I will suggest that etiologically it is of almost as much importance as the thyroid gland. May not the symptom-group of adiposis dolorosa result from a primary disease of either of those structures, the other being involved secondarily through their close inter-relation?"

Ballet<sup>8</sup> concluded: "Dercum's disease seems to result from a toxemia, the nature of which is undetermined, but which is neither alcoholism, syphilis, nor probably a thyroid intoxication. Perhaps the toxemia is caused by the defective functioning of a gland of internal secretion, which one we do not know. Whatever it is, according to this hypothesis, the toxemia causes both the lesions of the peripheral nerves and the encephalopathy."

Miquel<sup>129</sup> thought that the pathological findings "indicate a change in the nervous system, due probably to an autointoxication arising from disturbance of function of certain glands of internal secretion."

Strübing<sup>179</sup> found the cause of the disease in "disturbances of the nervous system," a "trophoneurosis."

Thimm<sup>182</sup> also thought that the origin of the disease "is to be sought for with great probability in certain central nervous causes."

These several views, it will be observed, center on disturbances of function of certain glands of internal secretion, the thyroid, pituitary, etc., or of the nervous system either primary or secondary to a toxemia arising from the glands of internal secretion.

As factors in the etiology the following have been mentioned: alcoholism, syphilis, traumatism, mental shock, disturbances of function of the generative organs, neuropathic heredity, etc.

#### DIAGNOSIS

Is adiposis dolorosa a clinical and pathological entity? The differential diagnosis of adiposis dolorosa, commonly represented as quite easy, hinges on the question whether this affection is a true morbid entity or merely a symptom-complex characterizing certain cases selected out of a larger, more general group that embraces clinical varieties, each showing a tendency to individualization, but still closely related by common features to all and constituting not several entities but a single complex entity. The former view has been adopted by Dercum,<sup>47</sup> who says: "Both the clinical findings and the results of the autopsies establish the

fact that adiposis dolorosa is a well-defined clinical entity." Nearly all of the text-books and most of the special writers on the subject seem to agree with Dercum in this opinion. To find any dissent from this view one must search the foreign literature.

Strübing,<sup>179</sup> while accepting the designation "adiposis dolorosa" as well chosen, regarded adiposis dolorosa, neuropathic edema, neuropathic pseudo-elephantiasis, multiple lipomatosis, and symmetrical diffuse lipomatosis, all as essentially one and the same process.

Thimm<sup>185</sup> said: "I come to the conclusion that in the painless diffuse and multiple circumscribed lipomata the same pathological process (*Grundprozess*) and the same genetic cause occur as in adiposis dolorosa and in painful lipomata and that the pain of the latter two conditions is to be explained solely by local conditions."

Fulconis<sup>68</sup> concluded: "The nosological limits of such a syndrome, i. e., adiposis dolorosa, are not yet clearly defined; its boundaries ought to be enlarged so as to include other forms of lipomatosis and pseudo-lipomatosis." "Certain cases of painful symmetrical lipomatosis associated with cerebral symptoms (asthenia and psychical disturbances) cannot be separated from Dercum's disease."

Cheinisse<sup>28</sup> concluded: "All the facts brought in review show that not only 'is Dercum's disease related to the other forms of lipomatosis of nervous origin,'<sup>167</sup> but also that it by no means constitutes a new morbid type, since in its essential characteristics it blends itself with the painful symmetrical lipomata."

Miquel<sup>120</sup> concluded: "There has been described for several years a certain number of nervous edemas still incompletely classified, from which it has been attempted to differentiate adiposis dolorosa. These several morbid conditions, which both from the pathogenic and the clinical point of view show an undoubted analogy, have been studied recently under the names *oedème névropathique*, Mathieu, 1893; *oedème segmentaire*, Debove, 1897; *trophoedème chronique*, Meige, 1899; *pseudo-oedème catatonique*, Dide, 1903.

"Adiposis dolorosa ought to be brought into the class of these different pathological conditions and it does not seem to constitute a well-defined clinical entity.

"All these morbid conditions have a common origin, in changes in the nervous system and in the different glands of the vascular system.

"They are probably, then, only varieties or stages of the same affection which constitutes the category of *dystrophies cellulo-conjonctives vasculaires* (Dide)."

With the view that adiposis dolorosa does not constitute a distinct clinical or pathological entity, but is at the most a mere syndrome or symptom-complex characterizing one end of a series of cases of which the several members or varieties share in different degrees a more or less common symptomatology, I fully agree. The evidence supporting this view will be developed in considering the other clinical groups of cases.

#### GROUP II. OBESITY, ADIPOSITY

It would be easy to collect from the literature a series of cases of obesity varying in symptomatology from normal to typical adiposis dolorosa. Every step in the upward gradation of symptomatology could be found. Every possible combination of the presence or absence of the different symptoms of adiposis dolorosa could be shown. If one examines the cases reported as adiposis dolorosa, he will find many instances of simple obesity plus one or more of the symptoms of adiposis dolorosa, but falling far short of the typical picture of that affection as described. If one systematically examines his hospital cases of obesity, he cannot fail to observe in them a complexity of constitutional symptomatology; of the four cardinal symptoms of adiposis dolorosa he will find asthenia frequent and of every grade; mental symptoms, while not common in major degree, will be found frequent in the minor form of simple nervousness, irritability, depression, stolidity, stupidity, hypochondria, etc.; pain and tenderness will not be found rare; and the accessory symptoms of adiposis dolorosa will be found in great variety. It will be observed also that the fat in extreme obesity is often disposed over the body irregularly and in places feels nodular, lobulated, like a "bundle of worms," etc., as described in adiposis dolorosa. Furthermore, simple obesity is frequently associated with nervous, neuralgic, arthritic and metabolic disturbances, both personal and in the antecedents, as is adiposis dolorosa. The development of obesity with asthenia and nervous manifestations after the menopause needs only to be mentioned, and the effect of thyroid therapy is well known.

Pain or tenderness is not uncommon in the fat of normal or only slightly fleshy people, if one's attention is directed to this point, as remarked by Osler.<sup>(c)</sup> Gently pinch the fat of rotund, well-nourished people and many of them will be found more than ordinarily tender. Percussion in the course of routine examination brings out the same fact. Painful tender flesh with a marked tendency to bruising, in the absence of any obesity whatever, occurs even in childhood and persists throughout

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(c) Personal communication.

life, and, furthermore, this peculiarity is exhibited as a trait of heredity, as shown in Patient 3 and her two daughters and in Patient 5 and her three sisters and one daughter. In pronounced obesity similar tenderness has been observed very commonly. Fressineau<sup>66</sup> says: "It is not rare to find in the obese slight pain on pressure of the fatty tissue." Mitchell<sup>130</sup> is reported as saying: "It should be emphasized that almost every case of excessive fatty deposit presented varying spots of tenderness, often in fixed positions. . . ."

On the other hand, instances of adiposis dolorosa, so reported, are numerous in which one or more of the cardinal symptoms are lacking. Eshner<sup>62</sup> observed: "There is no obvious reason why pain should necessarily be associated with the condition of fatty accumulation, and the case herein reported may be looked on as belonging to the same class [adiposis dolorosa], but without marked pain." Roberts<sup>163</sup> patient had no tenderness and had spontaneous pain only in the left leg, and that due perhaps to previous fracture. Case 7 presents three of the four cardinal symptoms of adiposis dolorosa, namely, adiposity, asthenia and mental symptoms (insanity), and in marked degree, yet lacks completely pain and tenderness in the abnormal fat. Case 8 presents three of the four cardinal symptoms, but lacks abnormal adiposity! Fressineau<sup>66</sup> pointed out that asthenic and mental symptoms, one or both, may be lacking. Strübing<sup>179</sup> made the same observation, and in general his cases failed to show mental symptoms or asthenia beyond that resulting from the incapacity produced by the local fatty deposits. Spiller's<sup>176</sup> Cases 2 and 3 showed no asthenia, no mental symptoms. Three of my cases (2, 3 and 4) showed no mental changes beyond irritability or simple nervousness, and two (5 and 9) presented a normal mentality. Similarly asthenia was slight, amounting only to readily induced fatigue in Cases 3 and 5 and was entirely lacking in Case 4. Patient 9 showed moderate obesity, moderate tenderness, no more asthenia than was explainable by the incapacity resulting from chronic arthritis of the knee and ankle joints, no mental symptoms. Similar instances abound in the literature.

Anders<sup>4</sup> has described under the title "adiposis tuberosa simplex" cases of common obesity with separate fatty lumps embedded in the general subcutaneous fat, felt on deep palpation, and characterized by varying degrees of tenderness and pain in the lumps and disappearance of the lumps with the reduction of the general fat under treatment. Such cases demand no special designation and only illustrate the possibilities of variation in the clinical picture of simple obesity. Similar

instances of the mixing of types of fat deposit in the same case are seen in Dercum's syndrome and in nearly all of the clinical groups to be described.

GROUP III. NODULAR CIRCUMSCRIBED LIPOMATOSIS, SOLITARY, MULTIPLE, OR SYMMETRICAL

The next obstacle to considering adiposis dolorosa an entity is encountered in certain cases of this group, presenting a symptomatology similar in every respect to that of adiposis dolorosa as originally described. This fact was soon recognized and frankly met by including such cases within the classification of adiposis dolorosa, as already indicated in Vitaut's classification. In fact, the single case personally observed by Vitaut (Observation 12) was one of multiple, nodular, painful lipomata. Dercum promptly accepted Vitaut's classification, as almost all later writers have also done. This acceptance of painful simple lipomata within the meaning of adiposis dolorosa seems, therefore, to remove such cases from controversy or further consideration in this connection, but it remains to show that pain is only one of many constitutional symptoms that may characterize simple lipomata and that all the other symptoms of adiposis dolorosa, one or many, may be found in varying degree and combination in individual cases of simple lipomata. We can, then, better appreciate the fact that individual cases of this group that happen to conform to the description of adiposis dolorosa by the occurrence of pain do not constitute thereby an entity, but merely a variation in a complex constitutional symptomatology.

Koettnitz<sup>97</sup> was perhaps the first writer to emphasize the occurrence of constitutional symptoms in simple lipomata. He divided lipomata into two classes, cases with symptoms and cases without symptoms. As examples of the first class he collected fourteen cases exhibiting constitutional symptoms, especially nervous manifestations, including pain, menstrual disturbances, and rheumatic or rheumatoid symptoms. These general symptoms as well as the symmetry of distribution of the lipomata in certain cases, stamped the process as a trophoneurosis, he thought. Later Thimm,<sup>155</sup> Spitzer<sup>157</sup> and other writers also called attention to the constitutional symptoms of lipomatosis.

Simple lipomata vary in different cases from a condition absolutely symptomless to one with marked constitutional symptomatology, including the full picture of adiposis dolorosa, as will be shown in the following abstracts of cases personally observed and in the literature:

LYON (CASE 13).—Multiple nodular lipomata; absolutely symptomless.

LYON (Case 14).—Solitary, circumscribed, soft lipoma; rheumatic symptoms only; son has multiple lipomata (heredity).

LYON (Case 15).—Multiple nodular lipomata; rheumatic symptoms only; father has a solitary lipoma (heredity).

LYON (Case 16).—Symmetrical nodular lipomata, painful and with black-and-blue discoloration only at the time of the first appearance of each tumor; inflammatory rheumatism, neuralgia. Father had painless symmetrical lipomata in the forearms, exactly as in the patient's case (heredity).

LYON (Case 17).—Symmetrical nodular lipomata, sciatica, "rheumatism;" local pain before the appearance of only one of the early lipomata.

LYON (Case 19).—Solitary, small, nodular lipoma, tenderness on pressure and spontaneous pains in and radiating from the lipoma in paroxysms, rheumatic symptoms, no other symptoms.

CHEVERS.<sup>29</sup>—Multiple lipomata, without symptoms; same condition in father and sister (heredity). (Reported as adiposis dolorosa.)

HAMMOND.<sup>50</sup>—Multiple lipomata, painful, no other symptoms; sister has same condition (heredity). (Reported as adiposis dolorosa.)

LYON (Case 18).—Multiple nodular lipomata, marked tenderness present in some, absent in other tumors, paroxysmal radiating pains, blueness over the tumors, slight nervousness, no asthenia or other symptoms.

KOETTNITZ (Case 1).—Symmetrical nodular lipomata. Woman, aged 65; at 26 gave birth to a child and thereafter she menstruated only three times; in place of the menses there appeared attacks of severe pains in the arms, legs and trunk and at the same time lumps in the parts of the body attacked by pains; these lumps grew larger and more numerous with each monthly attack of pains; at 54 the pains and formation of new tumors ceased.

SPITZER.<sup>177</sup>—Painful, symmetrical, nodular lipomata, asthenia, itching over the entire body, no other symptoms.

WEISS.<sup>198</sup>—Multiple lipomata, great variation in the tenderness and the spontaneous pain in the different tumors, great variation in the size of the tumors from time to time, no other symptoms. (Reported as adiposis dolorosa.)

WEISS.<sup>168</sup>—(Schlesinger's observation). Following an abortion, eruption of numerous, small, painless lipomata and development of pain in certain pre-existing painless lipomata. (Reported as adiposis dolorosa.)

RENON AND LOUSTE.<sup>160</sup>—Multiple lipomata, tenderness and spontaneous pain in the tumors, fatigue, slight mental changes. (Reported as adiposis dolorosa.)

HALL AND WALBRACH<sup>78</sup> (Case 1).—Multiple nodular lipomata, painful to pressure and spontaneously, ready fatigue, neurasthenia, hyperchlorhydria, rheumatism. (Reported as adiposis dolorosa.)

HALL AND WALBRACH<sup>78</sup> (Case 2).—Solitary lipoma on right hip, developing a few months after a blow at the same point (traumatism), painful to pressure and spontaneously, pain shooting upward to the tumor caused by pressure on the right heel, redness and blueness over the tumor, confinement to bed, mentality irritable and duller than formerly. (Reported as adiposis dolorosa.)

LYON (Case 20).—Multiple lipomata, slight asthenia, slight dementia, no pain, chronic "rheumatism."

DEBOVE.<sup>40</sup>—Symmetrical, nodular lipomata, slight tenderness varying in the different tumors, so slight that the patient made no complaint of it and denied pain on pressure though the writer thought that he demonstrated its presence, no spontaneous pain, asthenia (bed-ridden), dementia, herpes zoster, Heberden's nodosities.

VITAUT<sup>162</sup> (Observation 11, by Galland and Garand; reported also by Garand<sup>70</sup>). Symmetrical lipomata in forearms, painful cramps in forearms, rheu-

matoid pains in shoulders, rheumatism, no asthenia, no mental symptoms. Marked reduction in size of all the tumors, some almost disappearing, and complete disappearance of pains from thyroid treatment continued for eight months. (Reported as *adiposis dolorosa*.)

VITAUT<sup>192</sup> (Observation 12).—Symmetrical lipomata, pain and tenderness in tumors increased by exercise, blueness over tumors, slight asthenia, no mental symptoms except quarrelsomeness, thyroid enlargement, some reduction in the size of some of the tumors and in the pains from thyroid treatment. (Reported as *adiposis dolorosa*.)

KOETTITZ<sup>97</sup> (Case 2).—Symmetrical lipomata, no tenderness or spontaneous pain in tumors, marked asthenia, restlessness and anxiety, vertigo, fainting spells, ataxia, rheumatic pains in limbs and in joints of hands, knees and feet, migraine, goiter; development three years after menopause.

THIMM.<sup>185</sup>—Multiple lipomata, some painful, others not painful, blueness over tumors, fatigue, marked asthenia, no mental symptoms, headache, arthralgia, cramps, spasms and twitchings in limbs; growth of tumors preceded by local pains. (Reported as *adiposis dolorosa*.)

ALSBERG.<sup>3</sup>—Multiple lipomata, tenderness on pressure in the tumors, pains in arms and legs, fatigue, loss of strength, no mental symptoms, paresthesia, hoarseness, disturbance of speech, loss of sexual desire; growth of tumors preceded by local pains.

ESHNER<sup>61</sup> (Case 2, Dercum's observation).—Female, aged 36 years, had a severe fall followed by unconsciousness. Mi-carriage two weeks later. About six weeks later "seven or eight small swellings, varying in size from a small marble to a walnut, soft to the touch and apparently made up of fatty tissue," appeared on the left forearm. "These were exceedingly painful and tender on pressure." On examination nineteen months after the accident, there were also found on the lower portion of the back and in the sacral region several large, diffuse swellings, soft, painful and tender on pressure. General asthenia, pain in different parts of the body, headache, vertigo, tinnitus aurium, insomnia, indigestion, palpitation, hyperidrosis, increased micturition, etc.

SPILLER<sup>170</sup> (Case 1).—Female, aged 29; at 22 severe attacks of pain in right foot, at 25 swelling of right ankle and right leg just above knee, followed later by painful swelling of the whole right leg. The right leg, thigh, buttock and hip generally enlarged and containing both nodular and diffuse fatty masses. Over right iliac crest a diffuse, orange-sized, fatty mass with a "worm-like" feel. On left forearm one small nodular lipoma. The several tumors were all painful to pressure and subject to paroxysmal pain and swelling; some painful areas in right leg; no obesity, no asthenia, no mental symptoms, no menstrual disturbances; one attack of rheumatic pains. (Reported as *adiposis dolorosa*.)

ALGER.<sup>2</sup>—Multiple, nodular lipomata, painful to pressure but not spontaneously, in a woman, aged 29, developing during past eight years; increase of weight during past three years from 130 to 206 pounds, the increase of adiposity being unequally distributed over upper arms, back, breasts, buttocks and thighs and sparing the face, forearms, hands, lower limbs and feet; no pain or tenderness in this fat; fatigue, asthenia, melancholia, paresthesia, deep pain in the bones, pigmentation, thyroid treatment ineffectual; growth of the nodular lipomata preceded by local pains. (Reported as *adiposis dolorosa*.)

ROGERS.<sup>104</sup>—In "the myxedema, or myxedematoid condition, following thyroidism or exophthalmic goiter . . . some of these cases suffer much from lipomata in various parts of the body, and indeed there is much which is suggestive of, if not identical with, the disease called *adiposis dolorosa*." Supplementing this statement in a personal communication Rogers writes: "My statements in refer-

ence to adiposis dolorosa are the results of my personal observation. Painful lipomatosis in more or less marked form has been common in my experience with these cases. I have tried all kinds of organ therapy and believe that thyroid feeding is the only kind of the least assistance, although I have lately had under observation two cases which seemed to follow thyroidism and these are to a considerable extent relieved of pain by feeding with the adrenal nucleo-proteid."

Similar cases in greater number could be produced, but enough have been cited to prove the assertion, above made, that simple lipomatosis is frequently characterized by constitutional disturbances varying from nothing or next to nothing to the full symptomatology of adiposis dolorosa. Between these limits every conceivable combination of symptoms is represented. Of the so-called cardinal symptoms of adiposis dolorosa, namely, pain, asthenia and mental symptoms, in addition to fatty deposit, all may be present, all absent, or any one or more may be present or absent. The so-called accessory symptoms are also represented in great variety and combination. So varied in these different cases are the several symptoms supposed to characterize adiposis dolorosa that it would be impossible in many instances to say whether cases could be classed as adiposis dolorosa or not.

For example, a tiny, solitary, encapsulated lipoma in the forearm (Case 19) is tender on pressure and subject to paroxysmal radiating pains in a patient without other important symptoms. Is this a case of adiposis dolorosa? If not, why, then, is a large solitary lipoma<sup>78</sup> on the hip, appearing after local traumatism, painful to pressure and spontaneously, confining the patient to bed on account of the pain, with a mentality irritable and perhaps duller than formerly, so regarded and reported?<sup>(d)</sup> Indeed the conception of adiposis dolorosa as an entity seems to be made untenable by the narration of the diverse and complex symptomatology of simple lipoma, as above sketched.

Special attention may be called to certain features of interest exhibited by this group of cases. Arthritic manifestations, called rheumatic, rheumatoid, arthralgic, etc., frequently characterize these cases, as Koettwitz pointed out. The same manifestations have been specially described in adiposis dolorosa, and, as will be shown below, characterize all the different groups of abnormal fat deposit. The development of

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(d) This case became the subject of a claim for damages on the ground that the lipoma, pain and disability all resulted soon after and directly from a severe blow inflicted by a hack upon the site of the subsequent tumor formation. The jury found a verdict for the defense on the testimony of two medical experts that the case was one of "adiposis dolorosa" of the nodular variety, "the black-and-blue appearance being recognized as an occasional occurrence in this disease"—a clear case of miscarriage of justice resulting from the misconception of certain symptoms constituting a disease entity.



lipomata consecutively to the establishment of the menopause occurred in several of the above cases. The same relation in adiposis dolorosa has been emphasized. Traumatism as an exciting influence is illustrated in both groups. Changes in the thyroid gland are found in both. Benefit resulting from thyroid medication in the entire symptomatology is shown in both groups. Local cyanosis, blueness, or black-and-blue discoloration over the tumors is common to both. Paroxysmal increase of pains and of the size and firmness of the tumors is a frequent symptom in both. The occurrence of local pain at the site of subsequent tumor formation is shown in both. The mixing of types of fat deposit, diffuse and nodular, in the same case is exhibited in both groups. The influence of heredity, previously not much considered, is shown in both groups and will be specially considered in reference to all groups below.

One other point may be mentioned in this place in passing. The rule that lipoma once removed never recurs locally, a view generally held, is shown to have exceptions by Cases 14 and 18.

GROUP IV. DIFFUSE SYMMETRICAL LIPOMATOSIS WITH PREDILECTION FOR  
THE NECK ("FETTHALS," MADELUNG; "L'ADÉNO-LIPOMATOSE  
SYMÉTRIQUE À PRÉDOMINANCE CERVICALE,"  
LAUNOIS AND BENSAUDE)

As this variety of lipomatosis has received very slight and only recent recognition in the United States, a brief summary of its characteristics and references to the important articles in the literature will be given.

The earliest observation was made by Brodie<sup>20</sup> in England, in 1846. Baker and Bowlby<sup>7</sup> in England, in 1886, reported ten original observations and three cases from the literature, and Williams<sup>202</sup> in 1890, reviewed thirty-two cases, including four personal observations. Madelung<sup>113</sup> in Germany, in 1888, described the affection under the name *Fetthals*, collecting thirty cases from the literature and adding three personal observations. Madelung's paper was the first systematic treatise on the subject. Margais,<sup>116</sup> in 1894, published the first systematic description in France. In 1898, 1900 and 1901, Launois and Bensaude<sup>100, 101, 102, 103</sup> in France published personal observations, abstracted and illustrated many cases from the literature, and more than any other writers gave prominence to and caused recognition of the affection, describing it under the title *l'adéno-lipomatose symétrique à prédominance cervicale*. They succeeded in finding references to more than eighty cases in the literature. Shortly thereafter there appeared from Paris three theses on this subject, by Rehns,<sup>156</sup> in 1898, Tapie,<sup>154</sup> 1899, and Quéry,<sup>153</sup> 1902, all inspired by Launois and Bensaude.

In the United States, Warren,<sup>194</sup> in 1895, was the first writer to report a case with a recognition of its special features. In 1907, Collins<sup>32</sup> reported several cases, and, in 1908, Mills<sup>128</sup> reported a single case, and both writers reviewed the subject. Single cases, without recognition of their special characteristics, have been reported by Huckins,<sup>89</sup> in 1889; Adler,<sup>1</sup> 1893; Rosenstirn,<sup>166</sup> 1893 (the same case as reported by Adler); Kiliani,<sup>94</sup> 1909; and Johnson,<sup>93</sup> 1909. Coplin<sup>33</sup> has also mentioned a case; Louis B. Wilson<sup>(c)</sup> of Rochester, Minn., has seen cases at the clinic of the Mayos; George Blumer<sup>(c)</sup> has recently seen a case in Albany, N. Y., in consultation with Arthur W. Elting; and Grover W. Wende<sup>(c)</sup> of Buffalo is acquainted with a typical example. Several other American cases,<sup>15, 43, 46, 47</sup> reported as *adiposis dolorosa*, probably belong to this group (see abstracts below).

Madelung regarded the condition as a "special clinical form" of lipomatosis, not to be classed with simple multiple lipomatosis. Margais regarded it as a "well-determined affection." Launois and Bensaude represented it as a distinct entity with a special pathology, although admitting that "perhaps symmetrical adenolipomatosis, adenolymphocele, supraclavicular pseudolipoma, segmentary edema of Debove (neuropathic pseudo-elephantiasis of Mathieu) ought to be grouped in the same morbid series." Later writers have nearly all followed the opinion of Launois and Bensaude and represented the disease as a distinct morbid entity with a special pathology (see below).

The disease is described by Launois and Bensaude<sup>102</sup> as possessing three chief characteristics, symmetry, diffuseness and special localization of the fatty tumors. The symmetry is pronounced, but the appearance of the two symmetrical tumors is not necessarily simultaneous. The growths are not circumscribed or encapsulated, but diffuse, fusing with the surrounding fat tissue. The location of the tumors indicates a special predilection for the neck, beneath the chin, nape of the neck, base of the neck, preauricular, postauricular, etc. In addition to the neck, other parts of the body are usually invaded, in twenty-one out of thirty-three cases in Madelung's series. The location of the first tumors varied. They appeared on the trunk or extremities before the neck by intervals of two years (Langer<sup>99</sup>), three years (Bryk<sup>21</sup>), eight years (Henningsen<sup>83</sup>), twelve years (Bondet,<sup>16</sup> Fulconis<sup>68</sup>), nineteen years (DuCastel<sup>54</sup>). The face, hands and feet are usually spared,<sup>102</sup> although in one case each a tumor was present on the back of the hand (Williams<sup>202</sup>), on the tip of the nose (Bondet,<sup>16</sup> Fulconis<sup>68</sup>), and at the point of the chin (Lyon, Case 11).

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(c) Personal communication.

The consistency of the tumors varies from soft, even semicystic, to firm; they may be irregular or indistinctly lobulated and even feel like a varicocele, mamma, or "bundle of worms." On deep palpation small firm lumps or "nuclei"<sup>102</sup> are sometimes felt. In some instances the tumors are described as mixed or of different varieties, some clearly diffuse, others circumscribed lipomata (Du Castel<sup>74</sup>), common subcutaneous fibro-fatty tumors (Hutchinson<sup>90</sup>). The size and consistency of the tumors have been repeatedly described as subject to spontaneous fluctuations. They have never been observed to disappear completely,<sup>102, 113</sup> although in a few instances they have become almost unrecognizable. An exception to this rule is perhaps found in the case reported by Kiliani,<sup>94</sup> who said that "one large lipoma of the abdomen had disappeared spontaneously." After excision they never recur locally, although new formation may develop from the periphery (Madelung). Margais, however, says that they "often recur"—probably a mistake.

The duration of their growth varies from a few months to many years, as long as thirty-one years in Case 10. Like simple lipomata, they are not influenced by changes in the general nutrition.<sup>102, 113</sup> There is no necessary relation to obesity and in general the subjects are apt to be of normal weight, sometimes even spare.<sup>102, 113, 202</sup>

The first appearance of the tumors is usually after the age of 20, from 21½ to 58 years,<sup>102, 202</sup> although exceptions occur.<sup>39</sup> The disease began at puberty in Patient 11 and her two sisters.

Unlike simple lipoma and adiposis dolorosa, it occurs chiefly in the male sex, only occasionally in females. Instances in females have been reported by Bochoch,<sup>15</sup> Koenig,<sup>96</sup> Dartignolles,<sup>39</sup> Lejars,<sup>105</sup> Langer,<sup>99</sup> Launois and Bensaude,<sup>103</sup> Dercum,<sup>43, 46</sup> Bondet<sup>16</sup> and myself (Case 11); and other less typical instances in females have also been reported.

It may be pointed out that diffuse symmetrical lipomatosis, while exhibiting a distinct predilection for the region of the neck, does not invariably or necessarily invade that region. As shown above, the deposits have appeared on other parts of the body as long as nineteen years before any involvement of the neck was shown. In many instances similar diffuse symmetrical deposits of fat occur on the trunk or extremities exclusively, as in Case 12. Such cases cannot be differentiated from those presenting deposits in the neck. Furthermore, the deposits may be so diffuse and generalized as to cover the body more or less widely, as in the cases of MacCormac<sup>112</sup> (Clutton's observation), Baker and Bowlby<sup>7</sup> (Case 7), Jeanselme and Bufnoir,<sup>92</sup> Müller,<sup>134</sup> Lexer,<sup>109</sup> Langer<sup>99</sup> Dercum<sup>43, 46</sup> (two cases), Dercum and McCarthy,<sup>47</sup> Bochoch,<sup>15</sup> Morsaline,<sup>133</sup>

Nearly all writers have noticed the frequency of alcoholism in the history of the patients and many have attributed to it an etiological relation to the affection.

Previous writers have not emphasized the constitutional symptomatology of this form of lipomatosis, merely mentioning the occasional occurrence of general symptoms. I shall, therefore, direct attention to this subject. As in simple obesity and simple lipomatosis, a majority of cases present no marked constitutional disturbances. A minority, however, show the same general and special symptomatology exhibited by exceptional cases of obesity and of circumscribed lipomatosis, as already described.

The range of this symptomatology is illustrated in the following cases:

HENNINGSEN,<sup>83</sup>—Anidrosis.

ROSENSTERN,<sup>166</sup>—Anidrosis.

MÜLLER,<sup>134</sup>—Man, aged 43. Tachycardia, impotence, loss of sexual desire.

DUCASTEL,<sup>54</sup>—Man, aged 66, rheumatic, rheumatic family history. For years very marked pain on outside of right thigh.

LYON (Case 10).—Man, aged 71. Typical fatneck beginning at 40 years of age and developing uninterruptedly until death. From the age of 40, when the fatneck began, repeated arthritic attacks and attacks of double sciatica, continuing to the time of death.

WILLIAMS,<sup>202</sup>—Man, aged 40. Loss of memory.

SCHUCHARDT,<sup>170</sup>—Required to give up work on account of the weakening of mental faculties.

HUTCHINSON,<sup>90</sup>—Man, "excitable to the verge of insanity."

PÉAN,<sup>142</sup>—Man, aged 32. Duration of tumors two years. Loss of strength and rapid emaciation, coinciding with the constant growth of the tumors.

LANGER,<sup>99</sup>—Woman, aged 55. The disease began six years ago as "painful reddened tumors." "The reddening and pains soon disappeared."

BAKER AND BOWLBY,<sup>7</sup> (Case 8).—Man, aged 41. "For two years has noticed swellings in his neck and says that for the last year they have been very painful."

MARÇAIS,<sup>116</sup>—"One may find in certain patients pains of variable intensity, sometimes amounting to almost nothing, in other cases very definite and seated at well-determined points. One finds them specially in the form of lancinating pains and referred by the patient to a deep location; they seem to him to radiate from the angle of the jaw towards the clavicle below, the parotid region above, and the shoulder behind."

COLLINS<sup>32</sup> (Case 2).—Man, aged 36, alcoholic. Tumors for five years, not involving lower extremities except above Poupart's ligaments, and a "suspicious mass" on each quadriceps femoris. "His legs had been weak for about three years so that he had not been able to walk alone securely since his thirty-second year, and during this period he had suffered from severe cramp-like pains in the legs." paroxysmal. "For the past two months . . . he has been complaining of very severe stabbing, burning pains in the legs, from which he could not get relief. He stated that if he was touched with the point of a pin he immediately felt severe pains." Wasting of the extremities for twelve weeks, following vomiting and pains in the stomach. Emaciation, marked asthenia, increased patellar reflexes.

COLLINS<sup>32</sup> (Case 3).—Man, aged 55. For six years pain in the right arm and tenderness of the right shoulder-blade, also a burning sensation; occasionally similar pain in left shoulder and arm; pains paroxysmal, made worse by work. Tumors in painful areas. Considerable arteriosclerosis. History of alcoholism up to six years ago.

COLLINS<sup>32</sup> (Case 4). Man, aged 48. Tumors for ten years, in back of neck and over scapulæ. For nineteen months severe tearing and shooting pains in the lower legs, made worse by exercise. For six months following the beginning of the pains delirium, which "would sometimes cease for a brief time and he would be fully appreciative of his surroundings and of his condition, and then without attributable reason he would become confused. Sometimes this confusion would come on while he was in the street and he would lose his way." "Multiple neuritis, particularly of the lower extremities, and predominantly of the sensory type." "He admitted alcoholic habits."

LYON (Case 12).—Woman, aged 40. Diffuse symmetrical fatty deposits below ankles and on inside of knees and a single similar mass on right buttock, all slightly tender on pressure. Ready fatigue. Attacks of neuralgia or neuritis.

DALCHÉ.<sup>37</sup>—Weakness in arms and legs, asthenia, intelligence limited, memory lost; patient is apathetic, responds slowly, melancholic.

DARTIGNOLLES.<sup>39</sup>—Woman, aged 21. Neuropathic, severe migraine, sciatica, marked weakness in legs, general asthenia.

LAUNOIS AND BENSAUDE.<sup>100, 101, 102</sup>—Man, aged 32. Marked cachexia, marked asthenia, limited intelligence, distrust, unaccountable attacks of anger.

LAUNOIS AND BENSAUDE.<sup>102</sup> (Observation 22, Bouvet's case).—Man, aged forty-two years. Ulcer on back of right foot and a perforating ulcer on plantar surface of left foot with anesthesia of left foot. Exaggerated patellar reflexes. Epileptoid symptoms.

LAUNOIS AND BENSAUDE.<sup>102</sup> (Observation 23, Demon's cases).—Man, aged 48. Melancholia. Network of dilated veins over tumor of the neck.

EWALD.<sup>63</sup>—Man, aged 47, weight 198½ pounds. Pads of fat on the nape of the neck, in the region of the nipples, and about the umbilicus. "Drawing pains that suggested the pains of neuritis." Anidrosis, palpitation, dyspnea. Treatment by thyroid caused improvement in the general health, in the dyspnea and palpitation, and a loss of weight of 18½ pounds in six and a half weeks. (Considered by Ewald as Dercum's disease.)

MILLS.<sup>128</sup>—Man, aged 33. First appearance of tumors between three and one-half and four years ago. Attacks of acute articular rheumatism every winter for five years. "He has some feelings of distress or pain in the arms after hard labor, and at some examinations has complained of very moderate pain on pressure, particularly along the swellings in the upper arm. . . . He thinks he is not as strong as he was before the beginning of these swellings." Varicosities on legs and thighs. Defective hearing in both ears. Anemia: reds, 2,950,000; hemoglobin, 60 per cent.

STOLL.<sup>137</sup>—Man, aged 33, presenting typical fatneck. "The patient's mother has had for ten years a painless tumor on the shoulder. His mother's brother has had for several years painless tumors in the same places as the patient" (heredity).

LYON (Case 11).—Woman, aged 33. Typical fatneck began at puberty in herself and two sisters (heredity). Slight tenderness of the fatty deposits in the patient, not in the sisters, asthenia, deficient mentality, chronic sciatica from the beginning of the fat deposits, "rheumatism," hemorrhages, anidrosis, dysmenorrhea. One of the sisters with fatneck is insane. Chronic "rheumatism" in a brother and a sister, chronic sciatica in another brother.

DERCUM AND MCCARTHY<sup>47</sup> (Case 1).—Man, aged 39. After an acute illness, fifteen years ago, began to grow stout and later symmetrical deposits, "exquisitely painful to the touch," developed on the body. "He noticed also that as the deposits of fat grew he became excessively weak and easily fatigued." "His flesh would bruise very easily" and "slight blows would bring about black-and-blue marks," in two instances leading to ulceration. Similar black-and-blue marks occurred without trauma. Three years ago severe epistaxis. For five years major epilepsy. Height, 4 feet 10½ inches. Weight, 206 pounds. Diffuse symmetrical fatty deposits involving chiefly the trunk, abdomen, hips and buttocks, causing a grotesque contrast with the relatively small legs and arms. "There is also a dependent fold of fat beneath the chin." "Everywhere these masses of fat are exquisitely painful to pressure." "The skin is dry." "Irregular flushing, with here and there tendency to lividity, is also observed over various parts of the body. Here and there also the veins are somewhat prominent." Certain changes in the eyes. Death from erysipelas. Autopsy: "The testicles are undeveloped, the penis small, and there is a very scanty growth of hair on the pubis." Separate encapsulated lipomata embedded in the general fatty deposit. Hemolymph glands in the lipomata and in the diffuse fat. Interstitial neuritis of the nerve fibers in the subcutaneous fat. Adenocarcinoma of the pituitary body. Acute parenchymatous nephritis. Thyroid gland normal microscopically. Telangiectatic angioma and slight interstitial hyperplasia of the spleen. Anomalous arrangement of the convolutions of the brain. Fatty infiltration of the heart and liver. Right suprarenal gland twice the normal size, normal microscopically; left suprarenal not found. (This case was reported as one of adiposis dolorosa. The description and location of the fat deposits and the photographs seem to bring it within the group of diffuse symmetrical lipomatosis with predilection for the neck.) McCarthy,<sup>123</sup> in his latest publication on adiposis dolorosa, practically admits this, saying: "This forms a connecting link between adiposis dolorosa, adiposis cerebri, and symmetrical adenolipomatosis."

DERCUM.<sup>48</sup>—Woman, aged 61. Nervous prostration at 18 and again one year later. Present illness began ten years ago, manifested by weakness in the legs and in the back. "Some six or eight months after the beginning of the weakness in the legs, a painful lump of fat made its appearance at the back of the neck and immediately between and above the shoulder-blades. Subsequently, another painful mass of fat made its appearance over the left collar bone, and at various times thereafter numerous lumps, more or less diffuse in character, made their appearance on the left arm, on the right arm and, finally, over and about both knees. At the same time that the painful masses of fat made their appearance about the knees, the patient began to suffer from swelling in the joints. . . . Motion was attended with considerable pain. These symptoms reached a maximum amount of intensity about five years ago." "There is a lipoma on the back of the neck which is painful to pressure. There are painful supraclavicular lipomata on either side. There is a diffuse deposit of fat on the back, which is especially heaped up over the shoulder-blades. There are also very extensive and diffuse deposits over the abdomen, . . . arms, . . . forearms, . . . thighs and buttocks, . . . both knees." "In both arms the deposit of fat contains numerous lumps which are doubtless independent lipomata," similarly over the knees. These lumps are "painful to pressure." Face, hands and feet free. "The fatty deposits are everywhere painful to pressure, more so in some situations than in others." Mild dementia, marked asthenia, flushing of cheeks, forehead, palms and soles, extensive and widespread involvement of the joints, bursæ and tendons, patellar reflexes absent. (This case was reported as one of adiposis dolorosa, which admittedly it is. The diffuse lipomata on the back of the neck and in each supraclavicular space, etc., establish its identity with fatneck.)

DERCUM<sup>42</sup> (Case 3).—Female, aged 60, widow, no pregnancies. "Many years ago a lump appeared at the back of the neck." "At various times thereafter swellings made their appearance in various situations." Menorrhagia, occasional hematemesis and epistaxis. Menopause at 46. Mental impairment for two years. Anidrosis for years. Tumors: "Examination reveals soft, fatlike masses or swellings in various situations. Thus a large soft mass is found over either biceps, and others, somewhat smaller, over the outer and posterior aspect of either upper arm. Two large masses are found over the belly, separated above the umbilicus by a deep transverse crease. Another gives excessive prominence to the mons veneris. From the back of the neck, at its lower part, springs a big mass like a hump, while a diffuse swelling gives a cushion-like coating to either half of the back, and extensive deposits give unnatural prominence to either hip:" no deposits in hands, forearms, face, buttocks, thighs, legs and feet. The deposits varied in consistence, some being "firm and resistant," others "quite soft," "elastic" and "nodular." "Further it was discovered at once that these masses were painful to the touch, the patient complaining very much when only moderate pressure was exercised. This was especially true of the deposits over the arms and back of the neck. In addition, the patient complained of stabbing pains in the deposits, more marked in the regions just mentioned. She complained also of headache." Skin dry. Purpuric spots on forearms, thighs, legs and back. Cutaneous sensibility generally diminished; a few patches of anesthesia. "Patient is excessively feeble. For some two weeks past has been unable to walk. Lies, for the most part, in a quiet apathetic state, though when aroused answers questions intelligently, but slowly. Is, in addition, somewhat deaf." "Her dementia gradually deepened" until "she finally died in a comatose state." The autopsy showed enlargement, sclerosis and calcification of the thyroid gland, chronic nephritis, chronic gastritis, emphysema of the lungs, fatty infiltration of the heart and liver, slight thickening of the aortic and mitral valves, edema of the pia and brain. No microscopic examination. (This case was reported by Dercum as Case 3 in his first publication on "adiposis dolorosa.")

BOCHROCH.<sup>15</sup>—Woman, aged 56. "There is a fatty deposit the size of an egg under the chin, which is painful to pressure." There are also diffuse symmetrical deposits of fat in the upper arms (fat-bags), breasts, abdomen, hips and thighs, everywhere decidedly painful to pressure. "Constant, sharp, shooting pains in the arms and hands. She is quickly fatigued, and presents symptoms of a neurasthenic character." "The asthenia is typical in degree." "The mental symptoms are also typical, though they are not pronounced." "Her memory is impaired." She weighed less than 100 pounds at 19 years of age, when she was married; her present weight is 236 pounds. "Shortly after her marriage she noticed an accumulation of fat over both hips and over the upper parts of her arms and legs." Menopause six years ago. "Seven or eight years ago she noticed that she became easily bruised, a blow of the slightest intensity causing pain, attended by black-and-blue discolorations." One child is feeble-minded. "The case presents the four cardinal symptoms noted by Vitaut." "The case must be classified in the group termed by Vitaut the localized diffuse form." (This case was reported as a case of *adiposis dolorosa*. It is certainly such a case. The "fatty deposit the size of an egg under the chin" and the diffuse symmetrical deposits elsewhere also bring this case within the group of fatneck.)

BONDET<sup>16</sup> (also reported by Fulconis<sup>68</sup>).—Woman, aged 50. Severe traumatism on head and back at 38 years. At 38 left salpingo-ovariotomy, followed five or six months later by pains on inner side of left leg, just above knee, and after a few months by a tumefaction at the site of the pains. Similar phenomena in the right leg at the corresponding location and later by degrees in other parts of the body, always symmetrical. Menses ceased at 44 and thereafter the disease progressed

more rapidly. The pains were spontaneous, tingling and stabbing, localized in the tumors and also radiating along the course of nerves, paroxysmal, varying in intensity. The intensity of the pains diminished with the growth of the tumors. Tenderness to pinching or light pressure over the tumors. Location of tumors: legs, inguinal folds, buttocks, arms, shoulders, supraclavicular fossæ, submaxillary, preauricular, point of nose. Character of tumors; diffuse, ill-defined limits, feel doughy, pinching tumors cause ready ecchymosis. Marked asthenia, marked mental phenomena, change of character, attempt at suicide. Vasomotor instability indicated by repeated attacks of epistaxis and frequent flushing of the extremities. No obesity. Treatment by iodine and x-ray resulted in marked reduction in the size of the tumors and improvement in all the symptoms. The tumors on the neck and face appeared twelve years after those on the legs. (This case was reported as one of Dercum's disease. The preauricular and submaxillary tumors which finally appeared establish its identity with fatneck.)

MCMULLAN,<sup>120</sup>—Woman, aged 61, weight about 168 pounds, ten children, good health until five years ago, when she commenced to suffer from "numbness of the hands and arms, followed later by pain of an aching character, and subsequently by symmetrical fatty deposits in both upper arms." In the course of time the deposits "attained considerable dimensions," and the pain and numbness "increased to such an extent that the patient was unable to undertake even the slightest household duties." Later "pain and numbness were experienced across the back and chest and lately in the thighs just above the knees." For two years "severe hematemesis on several occasions and nine months ago uncontrollable hemorrhage following on extraction of a tooth." The patient is pale, sallow, "evidently suffers from debility," "is fairly bright and intelligent but complains of some loss of memory." Gums spongy; skin dry and harsh, perspiration very deficient; marked hyperæsthetic areas over both arms. "Large diffuse deposits of fat, pendulous and flabby in consistence, which involve both upper arms, and to a lesser extent the upper portions of the forearms," a similar deposit over the upper portion of the manubrium sterni, and "symmetrical fatty deposits over either scapular region and extending as low as the tenth or eleventh rib." No deposits below the waist-line; legs slender. No deposits in the neck, but the photographs show that the diffuse deposits in the arms continue up over the shoulders and across the back above the shoulders. Numbness, tingling and aching pains over the fat deposits and near the knees. "The pain is very much aggravated by using the limbs. The arms are tender wherever the fatty tissue is present, and even slight injuries cause bruising and discoloration."

Thyroidin was administered and "thus far, a period of scarcely two weeks, the result has been very satisfactory. The pains have almost disappeared, the numbness and tingling have been very much alleviated, and there is a distinct reduction in the size of the right arm of almost one-half inch. She herself states that she feels very much better, and can sleep and do a little work much better than she could for several months previously." (Reported as a case of *adiposis dolorosa*. The description and photographs indicate clearly that the case is one of symmetrical diffuse lipomatosis, belonging to the group here under consideration.)

After the citation of the above cases it would be superfluous to dwell further on the constitutional symptomatology frequently exhibited by this clinical group of cases. The remarks made on the symptomatology of simple obesity and of simple nodular lipomatosis might almost be transposed so as to apply here.



Pains, both spontaneous and induced by pressure, asthenia, mental symptoms, neuralgias, neuritis, arthritic and rheumatoid manifestations, vasomotor phenomena such as fluctuations in the size and consistency of the tumors, local blueness over the tumors, flushings, a tendency to black-and-blue discolorations, hemorrhages, anidrosis, the influence of the function of the generative glands on the development of the masses, changes in the thyroid gland, benefit from thyroid medication, the influence of heredity, the intermingling in the same case of different types of fat deposit, etc., are all represented in this group of cases, many of them so frequently and conspicuously as to eliminate the factor of chance as an explanation.

In other words, the constitutional symptomatology of general adiposity, nodular lipomatosis, and diffuse symmetrical lipomatosis is essentially one and the same. Within each of these clinical groups there are represented in individual cases every conceivable variation and gradation of symptoms from none at all to the full picture of *adiposis dolorosa*, so that cases of diffuse symmetrical lipomatosis have, in fact, been reported as *adiposis dolorosa*. Furthermore, there is not infrequently such an overlapping and blending of types between these groups that individual cases cannot be classified as belonging strictly to any one of them. In such cases the groups break down as entities and fuse into unity. In all there is a common process. In each there is a tendency to individualization, but not, however, strong enough to constitute morbid entities, but only clinical varieties.

*Pathology.*—Launois and Bensaude believed that they had established a special pathology for diffuse symmetrical lipomatosis by the presence of lymphoid or adenoid nuclei within the fatty masses, and accordingly they named the affection *adéno-lipomatose*, "adenolipomatosis." Subsequent writers have in general followed this conception of the disease. The only grounds worthy of mention on which Launois and Bensaude based their position were the presence in certain cases within the diffuse fatty tumors of small firm nodules, perceptible by palpation, and the finding in Hayem's<sup>22</sup> single case of small, blackish lymphatic clusters in the diffuse fatty masses. But these facts seem to lose all significance in this connection in view of the following: The small palpable lumps situated in the diffuse fatty deposits are nothing but invasions of connective tissue, as shown by operation in many cases. Exactly similar structures are common in all varieties of diffuse adiposity and diffuse lipomatosis, as already shown. The description of the small blackish lymphatic structures in Hayem's case corresponds to that of hemolymph glands, which they probably were. Similar bodies, identified as hemolymph

glands, have been found by McCarthy<sup>47, 122</sup> in two cases, both reported as *adiposis dolorosa*, although one of them probably belonged to the group of diffuse symmetrical lipomatosis. I have not been able to find in the literature any other cases of diffuse symmetrical lipomatosis in which lymphatic tissue, even traces of it, was found within the fatty deposits. It was not found in the cases of Dentu,<sup>42</sup> Schwartz,<sup>171</sup> Marçais,<sup>116</sup> nor, when specially searched for by careful microscopic examination, in the single cases of Desmons,<sup>(f)</sup> Dieulafoy,<sup>52</sup> Launois and Bensaude,<sup>103</sup> Lejars,<sup>105</sup> Mollard and Petitjean,<sup>131</sup> Morsaline,<sup>133</sup> Quéry,<sup>153</sup> Reclus,<sup>155</sup> Tuffier,<sup>189</sup> the two cases of Nélaton,<sup>(g)</sup> the two cases of Tapie,<sup>184</sup> and the three cases of Marotta.<sup>118</sup>

The development of lymphoid structures and especially hemolymph nodes in adipose tissue has been specially studied by Warthin,<sup>195</sup> who has observed them commonly in a wide range of conditions, e. g., fetal life, pregnancy, lactation, carcinoma, pernicious anemia, splenic anemia, leukemia, chronic inflammation, after splenectomy, etc. The occasional development of lymphoid or hemolymph structures in the fat deposits of diffuse symmetrical lipomatosis, *adiposis dolorosa* and allied conditions would appear, therefore, to be without great significance and would not warrant the assumption made by Launois and Bensaude of a special pathology connected with these glands and a special designation based thereon. The term "adenolipomatosis" should, therefore, be abandoned.

That this group of cases, like Dercum's syndrome, may show significant changes in the glands of internal secretion (pituitary, thyroid, adrenal, generative, etc.) is proved by the autopsy findings in two cases—the only instances in which the post-mortem examination included a careful microscopical investigation of these organs—reported by Dercum and McCarthy<sup>47</sup> and by Dieulafoy.<sup>52</sup> The findings in Dercum and McCarthy's case have been abstracted above. Dieulafoy's patient was a typical example of fatneck with wide distribution of the tumors. He presented no unusual symptoms and died from alcoholic cirrhosis of the liver with terminal tuberculous peritonitis. The autopsy showed: peritoneum, tuberculous; liver, cirrhotic and fatty; spleen, cirrhotic; pancreas, enlarged and cirrhotic; kidneys, congested and hemorrhagic; adrenals, congested; heart, dilated; thyroid, congested, adenomatous hypertrophy; pituitary, enlarged and congested; brain, congested, with typical dissemination of tuberculous granulations in the Sylvian and Rolandic areas; nervous system, "intact;" spinal cord, normal. The diffuse fatty masses infil-

(f) Cited by Dieulafoy,<sup>52</sup> p. 755.

(g) Nélaton: Cited by Pestemazoglu.<sup>144</sup>

trated deeply and extensively into the surrounding tissues. No traces of lymphatic tissue could be found anywhere in these masses, but connective tissue invasion was present in places.

GROUP V. NEUROPATHIC EDEMA, PSEUDO-EDEMA, PSEUDO-LIPOMA, LIPOMA, ETC.

It is necessary to mention a motley group of cases, little understood, still poorly classified, and described under many designations, e. g., *oedème hystérique* (Charcot, Warde); *oedème bleu des hystériques* (Charcot); *oedème blanc et bleu* (Charcot, Strübing); *oedème névropathique* (Mathieu); *oedème névropathique éléphantiasique* (Lourier); *oedème segmentaire* (Debove); *pseudo-oedème catatonique* (Dide); *pseudo-éléphantiasis névropathique* (Mathieu); *trophoedème chronique* (Meige); *lipomes symétriques d'origine névropathique* (Mathieu); *dystrophies cellulo-conjonctives vasculaires* (Dide). The cases described under these and similar designations represent various subcutaneous infiltrations that appear at first sight, many of them, quite unrelated to the subject of this paper. A more careful study, however, suggests that the pathological process concerned in these cases may be related to the development of fatty deposit. I shall refrain from expressing a personal opinion and confine myself to presenting the views of others, in abstract, on the relations of these various cases. Briefly stated, the assertion of the French writers is that the process is one of gradual transition from neuropathic edema or pseudo-edema to pseudolipoma and finally to true lipoma (Potain,<sup>148, 149</sup> Mathieu<sup>119, 120, 121</sup>).

It is strange, as Strübing<sup>179</sup> observed, that a considerable literature on this subject should have developed almost exclusively in France, "although here a certain one-sidedness has been exhibited in the view of its genesis. Charcot,<sup>26</sup> who in his observations found the infiltration of the skin especially in persons with functional disturbances of the nervous system, invested it, therefore, with the name *oedème hystérique*."

The earliest reference to this subject appears to have been made by Sydenham,<sup>182</sup> who observed: "Hysteria affects not only all the internal organs but involves also sometimes the external parts of the body and causes sometimes pains, sometimes swellings, the most distinct of which are those of the lower legs. The swelling neither yields to the impress of the fingers nor leaves a mark. The swelling so closely resembles dropsical swelling in size and surface that the patients are with difficulty convinced that it is not dropsy" (Charcot<sup>26</sup>).

Brodie<sup>(h)</sup> observed the same phenomena: "Repeatedly a swelling develops on the thighs and buttocks, either as a result of a turgescence of the blood-vessels or an infiltration of the cellular tissue, but principally as a result of turgescence of the blood-vessels, for the affected parts show no trace from the pressure of the fingers."

Edemas, described as "neuropathic" or "hysterical," have long been recognized in disease of the spinal cord, apoplexy, etc. (Strübing<sup>179</sup>). "Chronic elephantiasis-like edema may follow certain lesions of the central nervous system, cerebral hemorrhage, softening, acute myelitis, cerebral tumors, spinal cord diseases, ataxia, Parkinson's disease, sciatica, rheumatism and rheumatoid affections." "In short, one has encountered neuropathic edema following all the known lesions of the cerebrospinal system. neuroses, in cases showing no symptoms of nervous affection" (Lourier<sup>110</sup>).

Similarly, "the influence of the nervous system on the more or less abundant production of fat is, in fact, indisputable. Duchenne of Boulogne has called attention to adiposity of the subcutaneous connective tissue in paralytics" (Chantemesse and Podwyssotsky<sup>25</sup>). Landouzy<sup>98</sup> has pointed out the existence of localized subcutaneous adipose deposits in the muscular atrophies secondary to neuralgias, cerebral tumors, medullary lesions, etc. (Sellerin<sup>172</sup>). "Chronic edema evolves into sclerosis when it is inflammatory, into lipoma when it is neuropathic" (Milian<sup>128</sup>). "Recently published works of the *Société médicale des hôpitaux*: (Bucquoy,<sup>22</sup> A. Siredey,<sup>175</sup> A. Mathieu<sup>119</sup>) have established relations between neuropathic edema, pseudolipoma and lipoma, which constitute an uninterrupted series of anatomical conditions related to each other." "Symmetrical lipomata can be considered as examples of localized obesity" (Chantemesse and Podwyssotsky<sup>25</sup>).

According to Chuffart,<sup>30</sup> "the circumscribed edema that pits on pressure, the circumscribed edema that does not pit, and the true lipoma constitute three stages, the three degrees of evolution of one and the same tumor" (Lourier<sup>110</sup>). Mathieu<sup>119, 120, 121</sup> considers the process one of gradual transition from neuropathic or arthritic edema to pseudolipoma and finally to true lipoma. Potain,<sup>148, 149</sup> Desnos,<sup>48</sup> and Antony<sup>5</sup> hold the same view. According to Potain,<sup>149</sup> "the serous infiltration makes the ground for and excites the accumulation of fat and of fat cells" (Lourier<sup>110</sup>).

Cheinisse<sup>28</sup> believes that the different forms of lipomatosis and the neuropathic edemas cannot be separated, but constitute a common group of related cases. "For the explanation of the genesis of the elephantiae

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(h) Cited by Warde,<sup>110</sup> p. 11.

form of obesity, the same view must be considered as assumed for the genesis of symmetrical lipomata," i. e., a "trophoneurosis" (Strübing<sup>179</sup>). "Bucquoy<sup>22</sup> considers the diffuse symmetrical lipomata as being of nervous origin, due to a trophoneurosis, leading to dystrophies of the fat tissues which develop into lipomata" (Lourier<sup>110</sup>).

"Potain<sup>149</sup> has shown that in a rheumatic subject a transformation from edematous pseudolipomata to true fatty lipomata can take place; for Potain, in the firm edema, the serum does not develop in the interstitial spaces, but within the cells of the connective tissue" (Lourier<sup>110</sup>). According to Potain,<sup>149</sup> "arthritis is, in fact, a predisposing cause of these edemas, it is important to note. Most of the subjects who show nervous edemas are arthritic or rheumatic; often they are subjects of hereditary gout" (Lourier<sup>110</sup>). "I, too, have been struck by the relatively frequent coincidence of such joint affections and the infiltrations of the skin" (Strübing<sup>179</sup>).

Lourier<sup>110</sup> concludes: "The vasomotor disturbances that belong to the pathology of the neuropathic edemas can finally produce an elephantiasis in the affected region. The nervous edema develops as a complication in a great number of affections of the nervous system or more frequently in subjects of neuropathies. It is much more frequent in women than in men. Once developed, the condition of elephantiasis is incurable. . . . Neuropathic pseudo-elephantiasis and arthritic pseudolipoma have a certain degree of relationship: both are arthritic-neuropathic manifestations."

Miquel<sup>129</sup> concludes: "All these morbid conditions have a common origin, in changes in the nervous system and in the different glands of the vascular system. They are probably, then, only varieties or stages of the same affection which constitutes the category of *dystrophies cellulо-conjonctives vasculaires* (Dide). Adiposis dolorosa ought to be brought into the class of these different pathological conditions, and it does not seem to constitute a well-defined clinical entity."

Many of the French writers, following the view of Charcot, have laid much stress on hysteria as a cause of these infiltrations. Charcot<sup>26</sup> said: "Not often do I find described a form of edema, which we may call the pale edema of hysterics (the white edema of Sydenham), which in its changes resembles hydropsical edema except for the fact that in this latter, at least as a rule, a mark is left by the impression of the finger. Just as rarely have I found mentioned another form of edema, which, like that of Sydenham, presents itself as a swelling, which does not yield to the pressure of the fingers, but which differs from Sydenham's form in two evident signs, namely, by a lowering of the local temperature and

by a blue-violet color, which, sometimes very dark, sometimes only lilac, gave its name to the blue edema (*l'œdème bleu*), which I have proposed, because the change of color, so to speak, strikes the eye more than any other fact."

Similarly Warde<sup>193</sup> concluded: "Among the trophic disorders of hysteria, one of the more important is edema, which can be of two kinds: white or blue. It develops in subjects with hysterical stigmata, showing a vasomotor diathesis. It is differentiated from other edemas by the firm consistence, the special color, the absence of serum. . . ." Strübing<sup>179</sup> said: "I have repeatedly found in these patients a reddish and bluish discoloration of the skin of the extremities, especially the lower legs and forearms. That these vasomotor disturbances are of accidental nature admits of no doubt, for with infiltrations of equal intensity they are sometimes present, sometimes absent." "Hysterical manifestations of various kinds frequently complicate the disease picture, especially in patients of the better class, but are entirely absent in others."

"Correspondingly Lourier<sup>110</sup> also gives a wider range to the etiology of this edema. 'One is especially impressed with the neuropathic edema as the result of all known diseases of the cerebrospinal system, as the result of neuroses, and finally in cases in which the patient shows no symptom of a nervous disease; but whether the edema occurs with one or another of these conditions the method of its onset and its clinical appearances are quite constant' " (Strübing<sup>179</sup>).

"Therefore, one must conclude, say Mathieu and Weil,<sup>121</sup> that always the same physiological mechanism is disturbed in spite of the variation of the precedent condition in the different cases" (Strübing).

Strübing<sup>179</sup> has reviewed very critically the relation of these so-called edemas to adiposis dolorosa and has established to his own satisfaction their essential identity. The same symptomatology may be shown in both conditions. As to pain and tenderness in the affected parts, they may be absent or present and in every degree of intensity, corresponding in general to the intensity of the process. Mathieu<sup>120</sup> has directed special attention to pain in neuropathic pseudo-elephantiasis both diffuse in the lower extremities and especially along the course of the sciatic nerves. Fluctuations in size and exacerbations in the intensity of the swellings and pains may occur (Mathieu,<sup>120</sup> Milian,<sup>127</sup> Strübing<sup>179</sup>). Dide<sup>51</sup> has reported marked benefit from thyroid medication both in the infiltrations and the mental condition. Puncture or incision of the skin over the infiltrations has been made in many cases without obtaining the fluid of edema. Strübing excised the subcutaneous fat in one of his cases and

found that it was not edematous, much more firm and compact than normal, and the fat cells very large as sometimes they are found in lipoma.

"The designation of Charcot, *oedème blanc et bleu*, is scientifically objectionable, because it emphasizes the idea of edema which is not applicable to the pathological condition present in the skin of this affection" (Strübing).

GROUP VI. CEREBRAL ADIPOSITY, "ADIPOSITAS CEREBRALIS," "DYSTROPHIA ADIPOSITO-GENITALIS," "SYNDROME HYPOPHYSIAIRE ADIPOSITO-GÉNITAL," FRÖHLICH'S SYNDROME, ETC.†

Although the association of cerebral tumor or other cerebral disease with general adiposity had been previously recognized, the present interest in this relation dates from the publication of Fröhlich's<sup>67</sup> paper in 1901. This writer reported the case of a boy of 14 years with certain localizing cerebral symptoms (optic atrophy) and in addition a condition of general adiposity and sexual infantilism (hypoplasia of the genital organs), leading to the diagnosis of tumor of the hypophysis, which was confirmed by a subsequent operation by von Eiselsberg.<sup>55, 56</sup> This and allied observations collected from the literature led Fröhlich to attribute the condition of adiposity and sexual infantilism to disease of the hypophysis and to regard this association of phenomena as constituting a new syndrome, to which later writers have applied the designations, *dystrophia adiposo-genitalis*,<sup>11</sup> *syndrome hypophysaire adiposo-génital*,<sup>104</sup> "Fröhlich's syndrome," etc. Many similar cases have since been reported. A few of these cases have been operated on successfully; von Eiselsberg and von Frankl-Hochwart<sup>56</sup> excised the hypophyseal tumor in two cases, including Fröhlich's original case, with the result that in each the delayed sexual signs subsequently appeared. In one of these cases a slight loss of weight (1.6 kg.) occurred after the operation, in the other some increase.

Subsequently Erdheim,<sup>59</sup> Bartels<sup>41</sup> and others reported cases presenting the clinical features of Fröhlich's syndrome with tumor involving the duct of the hypophysis (*Hypophysenganggeschwülste*), the infundibulum or overlying parts, but not the hypophysis itself, and were led

† The most important papers relating to the subject of *adipositas cerebialis* in its different aspects are the following: Fröhlich,<sup>67</sup> 1901; Erdheim,<sup>58\*</sup> 1904; Bartels,<sup>41\*</sup> 1906; Uhthoff,<sup>39</sup> 1907; Tandler and Gross,<sup>183</sup> 1908; Marburg,<sup>115\*</sup> 1908; Cushing,<sup>35</sup> 1909; Delille,<sup>41\*</sup> 1909; Launois and Cléret,<sup>104</sup> 1910. The best bibliographies of the subject are found in the above references that are marked with an (\*). A complete bibliography is also promised by Launois and Cléret in the forthcoming Paris thesis of E. Grahaut, entitled *Le syndrome hypophysaire adiposo-génital*.

thereby to suggest that the trophic disturbances of Fröhlich's syndrome were due not to lesion or irritation of the hypophysis, but rather of some unknown trophic center located in or near the infundibulum at the base of the brain. This suggestion was met by the counter-suggestion that in Erdheim's case and similar cases the hypophysis was indirectly affected in its secretory function by the pressure of the overlying tumor.

Later, in 1908, Marburg<sup>114, 115</sup> reported a case and collected a few other cases from the literature of tumor of the pineal gland associated with general adiposity, without evident gross or microscopic alteration of the hypophysis, and on these observations he advanced the hypothesis that the adiposity and certain other trophic phenomena (*i. e.*, genital hyperplasia) were related to disease of the pineal gland, as a trophic center.

In still other rare instances, tumors or other disease of the brain in general have been associated with marked adiposity and other trophic phenomena.

All such instances of adiposity have been grouped together, pending the determination of their ultimate etiological relations, under the general designation "adipositas cerebialis." Of the several groups of cases in this category, those belonging to the hypophyseal group—involving the hypophysis itself (Fröhlich's group) or its connection with the base of the brain (Erdheim's group)—are by far the most conspicuous and characteristic. Marburg<sup>115</sup> was able to tabulate thirty-five instances, in 1908, and since then many others have appeared in the literature. Instances of the other varieties are distinctly rare. Only a few of the forty-four cases of disease of the pineal gland collected by Marburg<sup>115</sup> presented any marked adiposity. Therefore, the advocates of the hypophyseal origin of the adiposity have been inclined to ignore the other cases in which the hypophysis was not involved by the tumor or to explain such cases as indirectly hypophyseal in nature by reason of a supposed secondary effect on the hypophysis by pressure.

The supposed relation of disease of the pituitary (or pineal) gland to adiposity or other dystrophy led to the proposal<sup>114, 115</sup> of a hypothetical scheme of explanation of the symptomatology, suggested by the analogy of the thyroid gland, as follows:

Dysthyroidism.....	{	hyperthyroidism	=	exophthalmic goiter.
		hypothyroidism	=	cretinism, myxedema.
		athyroidism	=	cachexia thyreopriva.
Dyspituitarism.....	{	hyperpituitarism	=	gigantism, acromegaly.
		hypopituitarism	=	adiposity, genital hypoplasia.
		apituitarism	=	cachexia hypophyseopriva.
Dyspinealism.....	{	hyperpinealism	=	adiposity.
		hypopinealism	=	genital hyperplasia.
		apinealism	=	cachexia pinealipriva.



I shall not enter here into a discussion of the views above briefly outlined, deferring this for consideration below under etiology, but it seems appropriate in this place to call attention to the possibility of more comprehensive relations of adiposity and genital hypoplasia to the different glands of internal secretion than is embraced in the conception of a limited hypophyseal etiology.

Acromegaly and gigantism (hyperpituitarism?) frequently exhibit wide-spread pathological alterations in the various glands of internal secretion besides the hypophysis. Hypoplasia of the generative glands (sexual infantilism) is especially common. General adiposity may also develop concurrently with acromegaly or gigantism, and "lipomas often occur in the skin" (Dock).<sup>53</sup> Wurmbrand<sup>263</sup> has reported an instance of acromegaly characterized by the concurrent development of adiposity, and in addition the case presented lipomata over the shoulder-blades. Strümpell<sup>180</sup> has reported a similar combination—acromegaly, general adiposity and a lipoma over the base of the neck in a young woman. Other instances of this association<sup>158, 159, 41</sup> will be mentioned below. In gigantism with sexual infantilism, "there is no case as yet on record in which the administration of pituitary gland substance has started the delayed sexual development" (Thomson).<sup>186</sup>

As already stated, Marburg<sup>114</sup> has attributed the adiposity in his cases to tumor of the pineal gland, as a trophic center.

Infantilism is common in diseases of the thyroid gland, i. e., myxedema, cretinism, and is cured in general with other manifestations by thyroid medication. Moreover, in the absence of frank signs of myxedema, infantilism associated with adiposity of the feminine type may occur and be cured by thyroid treatment. Hertoghe,<sup>85</sup> Brissaud,<sup>16</sup> Apert,<sup>6</sup> Meige,<sup>126</sup> Hutinel<sup>91</sup> and others have reported many instances. As is well known, myxedema and cretinism are not infrequently characterized by more or less adiposity, either general or localized, and distinct lipomatous formations are not rare. Rogers' observations in this connection have already been given (under Group III).

A pancreatic form of infantilism has been claimed by Bramwell<sup>15</sup> and Rentoul,<sup>161</sup> who have reported cases presenting also a certain degree of the feminine type of adiposity and persistent diarrhea. These patients were cured, after thyroid treatment had completely failed, by the continued administration of pancreatic extract; the diarrhea ceased and adolescence and normal growth became established.

Hypertrophic biliary cirrhosis in young people is not infrequently complicated by a condition of infantilism, in some instances with a cer-

tain degree of adiposity. Lereboullet<sup>107</sup> and other French writers have called special attention to this association.

Disease of the adrenal glands may also rarely exhibit the same association. Morlat<sup>132</sup> reported three instances of Addison's disease complicated with infantilism, one of which was greatly benefited by the prolonged use of adrenal preparations. Marchand<sup>(i)</sup> reported a case of hermaphroditism with atrophy of the ovaries and hypertrophy of the adrenals. On the other hand, adrenal tumors may be associated with excessive development of the genitals, hair and fatty tissue [Woolley, Bullock and Sequeira<sup>(j)</sup>], or even with general precocious development [Linser<sup>(k)</sup>].

In status lymphaticus, adiposity and hypoplasia of the genital organs are common and "a condition of infantilism may persist after the age of puberty" (Warthin<sup>196</sup>). In a large autopsy material Bartel<sup>10</sup> found this condition, which he calls the "hypoplastic constitution," often characterized by "adipositas universalis," genital hypoplasia, colloid hyperplasia of the thyroid, hyperplasia of the thymus, and other trophic disturbances; no mention is made of the finding of pathological changes in the hypophysis.

An intimate relation between the function of the generative glands and adiposity is well known and will be considered below, under etiology.

All the facts, above cited, seem to imply that not only the pituitary gland, but also many of the glands of internal secretion (pituitary, generative, thyroid, thymus, pancreas, adrenal, liver, pineal, etc.) may be concerned, directly or indirectly, in the production of adiposity and genital hypoplasia, symptoms which have been specially emphasized as characterizing hypophyseal tumor, i. e., Fröhlich's syndrome.

I have not had the opportunity to review critically the group of cases of Fröhlich's syndrome with reference to the special object of this paper. It is desirable that this be undertaken. The impression that I have received from a somewhat intimate acquaintance with the literature of these cases is that they do not constitute a separate entity, but are related both in symptomatology and pathology to the other groups of abnormal fat deposits. This view is based on the presence, in certain of these cases, of mental disturbances, asthenia, pain and various nervous, sympathetic and vasomotor symptoms and also on the fact, already presented, that autopsies in several cases of "adiposis dolorosa" have shown tumor or other changes in the pituitary body and atrophy of the generative

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(i) Dock,<sup>53</sup> p. 354.

(j) Dock,<sup>53</sup> p. 359.

(k) Dock,<sup>63</sup> p. 354.

organs (ovaries) and in one case reported as "adiposis dolorosa," and coming within the group of diffuse symmetrical lipomatosis, tumor of the pituitary body and atrophy of the testicles and penis.

In a case of "degeneratio adiposo-genitalis," reported by von Eiselsberg and von Frankl-Hochwart,<sup>56</sup> the patient operated on was mentally dull and had "diffuse pains over the ribs and the joints of the extremities."

White's<sup>200</sup> case, reported as "adiposis dolorosa," probably is essentially identical with Frölich's cases. Preceding the establishment at 12 of the menses, which remained quite irregular, the patient began to grow obese and at 13 weighed 280 pounds. Simultaneously with the development of the obesity, spontaneous paroxysmal pains appeared in different parts of the body, including the head and eyes. At 15 the patient's mind began to be affected and she had periodical attacks of dementia ushered in by epileptiform fits. At 22, when she was observed by White, she was excessively obese, markedly asthenic, mentally disturbed; the sensations for temperature touch and pain were impaired; and the masses of fat were very tender, so that she could not bear to have them grasped. Under combined thyroid medication and massage continued for nine months there was a loss of 70 pounds in weight with improvement of the mental condition. Compare also with this case that reported by Dercum and McCarthy,<sup>47</sup> abstracted above.

Renon, Delille and Monier-Vinard<sup>159, 41</sup> have reported the case of a man of 36, with retarded sexual development, scant growth of hair on the face, axillæ and genital region, intellectual torpor, polyuria, pronounced obesity, voluminous breasts, atrophy of the thyroid, enlarged sella turcica (observed by x-ray) and other tissue changes indicating acromegaly. Most of these phenomena had developed during the preceding two years. Located near the knee was a small lipoma, painful to pressure. The same authors<sup>158, 41</sup> have reported the case of a girl of 16, in whom had developed concurrently during the preceding four years the following complications: acromegaly, optic atrophy, frontal headaches, mental and cerebral symptoms, sexual infantilism and adiposity, especially of the trunk, irregularly lobulated in places and distinctly painful to slight pressure.

Case 11 of the series presented in this paper, belonging to the fatneck group, also throws light on this question. The disease began in this patient and her two sisters at puberty and reached its full development before maturity. In the case of the patient there was dysmenorrhea, imperfect mental development, asthenia, some tenderness in the fatty

masses, recurrent sciatica, anidrosis, hemorrhages, etc., and one of the patient's sisters having fatneck was insane.

Further, Fröhlich's syndrome varies widely in the different cases in the degree of adiposity and in the genital involvement. The adiposity varies from normal to excessive. Genital atrophy is not constant, being found in only twelve out of thirty-two patients that were examined at autopsy (Marburg).<sup>115</sup> Finally it may be pointed out that hypophyseal tumors may occur in association with a considerable variety of trophic disturbances<sup>(1)</sup> or even without any at all.

### CONSIDERATION OF THE COMBINED GROUPS

#### GENERAL SUMMARY

It has been attempted to show that the several groups of cases of subcutaneous fat deposit, whether diffuse or circumscribed, do not constitute clinical and pathological entities, but rather varieties in the expression of a common morbid process; that this process may involve a profound and wide-spread disturbance of the organism, with a resulting complex constitutional symptomatology; and that this symptomatology varies within wide limits, tending sometimes to more or less individualization and constituting thereby clinical varieties or groups of cases, not sharply defined.

There remains only to emphasize some of the characteristics in the symptomatology and to consider the etiology of the process.

*Age.*—No period of life is spared; childhood, adolescence, maturity and senility are all embraced in the period of inception of the process. A majority of cases occur in middle adult life, in women especially at the time of or shortly after the menopause.

*Sex.*—The sexes tend to be unequally represented in some of the groups; in the group of diffuse symmetrical lipomatosis with predilection for the neck (fatneck), males greatly predominate; in the group of circumscribed nodular lipomatosis, Grosch<sup>73</sup> found that solitary lipoma occurred in the sexes in the proportion of 100 males to 162 females and in general in this group females somewhat outnumber males; females also predominate greatly in the groups of adiposis dolorosa and neuropathic pseudo-edema.

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(1) Acromegaly, gigantism, dwarfism, acromegaly or gigantism with adiposity or lipomatosis, myxedema, cretinism, Addison's disease, general adiposity, genital hypoplasia, general adiposity and genital hypoplasia (Fröhlich's syndrome), general adiposity presenting Dercum's syndrome, diffuse symmetrical lipomatosis presenting Dercum's syndrome, etc.

*Fat Deposits.*—These may occur in any of the forms already described or in mixed forms.

*Pain.*—In all the groups, pain, both spontaneous and induced by pressure, may occur in the fatty deposits. Local pain may precede the development of these deposits of whatever type or variety. Exacerbations in intensity or paroxysms of pain may occur in all. Pain is not frequent in the group of diffuse symmetrical lipomatosis, but may occur and of an intensity equal to that seen in typical cases of Dercum's syndrome.

There are reasons for believing that the pain depends on the presence of a chronic, low-grade, interstitial neuritis of the small nerve fibers distributed in the fatty deposits. Microscopical examination of the painful fat showed this condition in five out of six autopsies on cases of Dercum's syndrome in which special examination was made, including one case that belonged to the group of diffuse symmetrical lipomatosis: in this case interstitial neuritis was found in the nerve fibers both of the diffuse fat and within certain circumscribed lipomata included in the diffuse fat.

Examination for nerve fibers within painful nodular lipomata has been made by Vitaut,<sup>192</sup> Rénon and Louste,<sup>190</sup> Weiss,<sup>198</sup> Spitzer<sup>177</sup> and myself (Case 19), without success. Thimm<sup>185</sup> identified doubtfully nerve fibers in a painful lipoma. Alsberg<sup>3</sup> positively succeeded in one case, and in Case 18 I found a definite small nerve bundle within a connective tissue septum of a very small painful lipoma, with changes interpreted as indicating a chronic interstitial neuritis.

Some writers, e. g., Strübing, Thimm, Spitzer, explain the pain as due to congestion or stasis in the fat deposits, causing mechanical interference (tension, pressure) with the surrounding nerves. This factor undoubtedly plays a part in the causation of pain, especially the paroxysmal pain accompanying exacerbations with increase in the size and consistence of the fatty masses. The marked amelioration of pain following profuse hemorrhage, in my Cases 2 and 3, would tend to support this view. Koettwitz, Riedel and other writers express the view that the lipomata are not primary and the pain secondary, but "both are the product of one and the same cause," i. e., a "trophoneurosis."

Finally, pain may be regarded as an accidental symptom, absent in the majority of cases, but present in certain cases of all groups. It is one of the many constitutional symptoms that characterize this process. Its presence in any case does not distinguish that case from similar cases without pain and does not determine an entity (*adiposis dolorosa*).

*Asthenia*.—This occurs in a minority of cases of all the groups and does not especially distinguish the cases with pain. It is one of the general symptoms.

*Mental Symptoms*.—These are extremely variable, inconstant, and may occur in cases in all groups. In the great majority of cases they are as good as wanting. When present, even in Dercum's syndrome, they are usually slight in the form of simple nervousness and only exceptionally reach the grade of the major psychoses. Even dementia, insanity, suicide, etc., may occur in cases of lipomatosis without pain.

The so-called *accessory symptoms* of Dercum's syndrome are exhibited typically and in great variety and combination in all the groups, as shown. Several of these symptoms that have been emphasized as characterizing adiposis dolorosa are prominent in the symptomatology of the other groups, including pigmentation of the skin, anidrosis, hemorrhages, local flushing with red or blue discoloration, tendency to bruising, paroxysms or exacerbations in the intensity of the process with increase in the size and consistence of the masses and in the pains, varicosities, tachycardia, headache, disturbances of sensation, etc.

*Arthritism, Rheumatism, Neuralgia, Neuritis.*<sup>(m)</sup>—These manifestations occur in the several groups of fatty deposit with such frequency and such close relation to the course of the disease that attention should be directed to them as symptomatic of the morbid process. Striking examples of this relation are seen in Cases 10 and 11, in one of which attacks of sciatica and in the other attacks of sciatica and articular pain and swelling began with the first appearance of the fatty masses and recurred thereafter at short intervals throughout life. The same symptoms are frequently mentioned in the family history of cases.

The occurrence of these symptoms can be no mere coincidence. They belong clearly to the symptomatology of the morbid process, related probably to disturbances of function of the glands of internal secretion.

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(m) In directing special attention to this group of symptoms some definition of the terms used is desirable. This is by no means easy as the manifestations cover such a wide range. The terms, "rheumatism," "rheumatic," "rheumatoid," "arthritis," "arthritism," "arthritic," "arthralgia," etc., refer to the many articular and periarticular manifestations which still defy scientific medical classification, *e. g.*, pain, stiffness, swelling, flushing, chronic structural changes, hypertrophic and atrophic arthritis, Heberden's nodes, etc., in short the whole array of articular manifestations short of acute rheumatic fever. The terms "neuralgia," "neuritic," "neuritis," "neuritic," carry their usual signification and imply no greater diagnostic accuracy than is permitted by the symptomatology of any given case. Greater accuracy of definition and statement is not warranted. The essential point is that these manifestations occur in many of the cases and seem clearly to belong to the general symptomatology of the trophic disorder.

Diamantberger<sup>49, 50, 197</sup> has called special attention to a certain degree of etiological relation between disturbances of function of the thyroid gland and "rheumatism,"<sup>(n)</sup> acute, subacute, chronic, and has claimed that thyroid therapy can cure these conditions in some instances. Several writers,<sup>(o)</sup> notably Léopold-Lévi and de Rothschild,<sup>106</sup> have corroborated this claim, especially as regards certain types of chronic "rheumatism." Morsaline<sup>133</sup> has reported cases of "chronic rheumatism" associated with symmetrical lipomata in the region of the affected joints in which, as the result of thyroid medication, not only were the articular manifestations benefited, but also "the lipomata about the joints were reduced in size and in some instances completely disappeared."

Similar arthritic and neuralgic manifestations have been described also, sometimes in recurrent attacks, in other conditions that are dependent on or related to disease or change of function in one or other of the glands of internal secretion, e. g., exophthalmic goiter, myxedema, cachexia strumipriva, Addison's disease, acromegaly, epilepsy, idiocy, obesity, diabetes, menopause, etc., and it should be remembered in this connection that chronic interstitial neuritis is not uncommon in some of these affections, notably in acromegaly. The "growing pains" and arthralgia of adolescence may be recalled in this connection, and the not infrequent development of Heberden's nodes and other forms of hypertrophic arthritis with the menopause.

*Heredity.*—A neuropathic family history has been noted frequently in all varieties of abnormal fat deposit, but direct heredity or the multiple incidence of the disease in families has been supposed to be excessively rare except in the form of common obesity. Either this opinion is erroneous—and I believe that it is, and because attention has not been directed to this relation—or my personal experience in this regard has been exceptional, for it is shown in no less than seven of the twenty cases, above reported by me, involving twelve different persons. In order to emphasize this relation, I shall present in abstract the different instances that have come to my attention, personal or from the literature, as follows:

LYON (Cases 14 and 15).—A father (Case 14), aged 52 years, had a solitary lipoma excised from his thigh at the age of thirty. It recurred at the same point and is now present, about the size of an orange. His son (Case 15), aged 26, presents multiple, partly symmetrical, circumscribed lipomata, which have been growing since he was 14 years old.

(n) Lancereaux and Paulesco, Parhon and Papinian, Viala, Claisse, Léopold-Lévi and de Rothschild, Sergeant, Ménard, Vincent, Aechiotté. Cited by Diamantberger,<sup>50</sup> pp. 336-337.

(o) Diamantberger<sup>50</sup> offers an ingenious explanation of the dual etiology of infection and thyroid perversion in these affections.

PETRÉN.<sup>146</sup>—Multiple symmetrical lipomata, symptomless, in a man aged 58 years. His mother had had multiple lipomata, not symmetrical.

MURCHISON.<sup>135</sup>—Multiple lipomata on the arms in corresponding positions in a father and two daughters. Nine sons were free.

REXARD.<sup>157</sup>—Subcutaneous tumors, which gradually increased in size, appeared over the whole body, except the face, palms and soles, in a previously healthy mother after weaning a child. The child, a boy, very poorly developed in mind and body, showed very similar tumors with about the same distribution. Petrén.<sup>146</sup> referring to this case, says: "The lipomatous nature of these tumors seems to me not to be beyond question." Possibly they were instances of von Recklinghausen's disease, neurofibromatosis.

LYON (Case 16).—Multiple, symmetrical nodular lipomatosis in a strong, healthy man of 49, first appearing at the age of 18. Each new growth was preceded by local pain followed in a few days by black-and-blue discoloration and then by the appearance of the tumor. History of multiple attacks of inflammatory rheumatism; neuralgia; phlebitis of the left saphenous vein. Marked rheumatic family history. His father had the same kind of fatty tumors, with the same distribution in the forearms.

CHEVERS.<sup>29</sup>—Multiple lipomata, widely distributed over body, symptomless except that "before each growth appeared he had an aching sensation at the spot which lasted until a shotty papule made its appearance" in a man aged 75. The disease began at the age of 40. "Typical lipomata." "Some of the tumors are as big as a child's head." The hands, legs below the knees, feet and face are spared. His "father had the disease, and died a hale and hearty old man." "One of his living sisters has the disease." Also, "two of his sisters and one brother have been subject to fits ever since they were 10 years old." (Reported as *adiposis dolorosa*.)

HAMMOND.<sup>50</sup>—Multiple lipomata in a woman, aged 61. They first appeared in the forearms when the patient was 35; subsequently also on the thighs and abdomen. Pain was a marked and persistent feature. Considerable tenderness to touch in the tumors. A sister, 40 years of age, was similarly affected. In her case the "disease started some years ago, in much the same manner, with local tumors in the arm, and fresh ones are gradually forming elsewhere. Here, again, pain has been a noticeable element." (Reported as *adiposis dolorosa*.)

BLASCHKO.<sup>14</sup>—Multiple lipomata, large and small, on different parts of the body, occurring in corresponding positions in a father, his sons and his brother, beginning in all at puberty. The female members of the family and the sons under the age of puberty were free.

REVERDIN.<sup>162</sup>—1. Symmetrical diffuse lipomatosis of the thighs in a woman, aged 20, and identical tumors in two sisters.

2. Similar lesions, similarly situated on the thighs, in another young woman and correspondingly in her mother.

STOLL.<sup>178</sup>—Symmetrical diffuse lipomatosis in back of neck, typical fatneck, in a man, aged 33. "The patient's mother has had for ten years a painless tumor on the shoulder. His mother's brother has had for several years painless tumors in the same locations as in himself."

LYON (Case 11).—Diffuse symmetrical lipomatosis, type fatneck, in a woman, aged 33, and similarly in two sisters, beginning in all at puberty and reaching maximum development before maturity. The patient was dull mentally, asthenic, had dysmenorrhea, recurrent sciatica, hemorrhages, anidrosis, and slight tenderness in the fat deposits, most of these symptoms dating from the onset of the lipomatosis. One of the sisters with fatneck was insane. Arthritic family history.



LYON (Case 2).—Dercum's syndrome, elephantiae and diffuse form, in a woman, aged 75, dating from the age of 25. A daughter, with symptoms of hysteria, developed in early childhood two lipomata, painless, symmetrically placed, one on each side of the back in the lumbar region, about the size of a hen's egg, which remained unchanged and symptomless until her death at 20 years of age.

LYON (Cases 3 and 4).—Dercum's syndrome, generalized diffuse and nodular mixed form, in a woman (Case 3), aged 55 years, whose flesh had always from early childhood been tender and painful and subject to ready bruising with black-and-blue discoloration. This peculiarity of tenderness and bruising of the flesh from early childhood has been equally shared by two daughters, aged now 34 and 37 years respectively. One of these daughters (Case 4) shows slight fat-bags in the upper arms, but otherwise no abnormality of fat deposit. She also presents many of the symptoms of Dercum's syndrome.

LYON (Case 5).—Atypical Dercum's syndrome, localized diffuse and nodular mixed form, in a woman, aged 64. Marked personal and family history of arthritism. Personal history of epistaxis, neuritis, cerebral attacks. Tenderness and bruising of the flesh from childhood, a peculiarity shared equally by three sisters and one daughter. During the past five years development of subcutaneous lipomata, painful spontaneously and on pressure, and during the same period loss of strength. During the past year increased adiposity over abdomen and hips. Normal mentality.

A cousin, son of the patient's father's brother, aged 51, is somewhat obese and presents symmetrical lipomata in the lumbar and dorsal regions, painful spontaneously and on pressure. The subcutaneous fat everywhere is slightly but definitely tender on pressure and has been markedly subject to easy bruising. Several attacks of cervico-brachial neuralgia; hyperhidrosis; headache; neurasthenic mentality; no asthenia.

SIEVERT.<sup>174</sup>—Type, adipositas cerebialis. Marked general adiposity, involving especially the breasts, abdomen, mons veneris and buttocks, associated with optic atrophy, occurring in both brother (aged 15) and sister (aged 9). No evidence of genital hypoplasia, enlargement of the sella turcica (x-ray), acromegaly, gigantism, or other trophic disturbances. Family history negative for obesity.

These cases illustrate the heredity or family incidence of circumscribed lipomatosis, solitary, multiple, symmetrical; of circumscribed symmetrical lipomatosis with the symptoms of Dercum's syndrome; of diffuse symmetrical lipomatosis, both involving the neck (type fatneck) and not involving the neck, some with and some without the symptoms of Dercum's syndrome; of diffuse adiposity with all or many of the symptoms of Dercum's syndrome; of adipositas cerebialis; and of mixed and crossed types. Certain of these cases are of such a character as clearly to exclude the factor of accident or coincidence and to require the recognition of heredity as the only reasonable explanation.

#### ETIOLOGY

Many views have been suggested to explain the morbid process in one or other of its forms, most of which may now be regarded as obsolete (e. g., the skin-gland hypothesis of Grosch,<sup>73</sup> the adenoid-gland hypothesis of Launois and Bensande<sup>102</sup>) or inadequate. The views, frequently advanced, that alcoholism, syphilis, rheumatism, traumatism, nervous

shock, etc., are causes are clearly inadequate to explain the great majority of cases. That such conditions may perhaps play some part as predisposing or exciting factors in the etiology of individual cases cannot be denied; and, indeed, there are good reasons for attributing to them such influence. Various infections and intoxications are known to have important effects on the peripheral and central nervous system and on the glands of internal secretion, e. g., thyroid, pituitary, adrenals. The relation of traumatism and nervous and mental shock to the development of adiposity and lipomatosis is too intimate and frequent to be dismissed as accidental. But, admitting the probability that these conditions may act in certain instances as predisposing or exciting factors, they cannot be accepted as operative and adequate in the cases as a whole.

Only two views have received wide acceptance, and these two may perhaps be resolved into one. According to these views, the process depends on primary disturbances of the nervous system or on disturbance of function or disease of one or more of the glands of internal secretion, producing secondarily a dystrophy or trophoneurosis through the agency of the nervous system. Most of the facts cited in support of a primary nervous cause apply equally to the other view, such, for instance, as the influence of heredity, the symmetrical distribution of the fatty deposits, and the general symptomatology evidencing a disturbance of function of the nervous system. It seems more in accord with the facts, so far as at present known, to accept the nervous hypothesis as modified by the second view, although, it must be admitted, such a position is only tentative and subject to revision. For it is impossible with our present rudimentary understanding of this complicated subject to distinguish clearly between primary and secondary etiological factors in the interrelation of the nervous system and the system of glands of internal secretion.<sup>(p)</sup> Probably these factors are primary or secondary only in a relative sense and vary in different cases.

#### THE GLANDS OF INTERNAL SECRETION—PITUITARY, THYROID, GENERATIVE GLANDS, ETC.

The facts that seem to incriminate these glands as the underlying cause of the pathological process may be summarized as follows:

In six autopsies on cases of Dercum's syndrome, in which the hypophysis was examined microscopically, it was found grossly diseased in three, microscopically altered in two, normal in one. In Fröhlich's syndrome also the hypophysis or its connections has regularly been found diseased.

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(p) For a discussion of this problem in reference to exophthalmic and other types of goiter, see papers by Marine and Lenhart,<sup>117</sup> and Rogers.<sup>154, 155</sup>

Operations on the hypophysis in Fröhlich's syndrome have in a few instances caused a marked effect on the symptoms.

Marburg's observations seem to indicate that tumor of the pineal gland<sup>(q)</sup> may be related to abnormal adiposity, although another explanation of these cases is possible, as already suggested.

The thyroid gland was found more or less altered in seven out of eight autopsies, normal in one, in cases of Dercum's syndrome. Therapeutically, thyroid substance has been found to benefit all forms of adiposity and lipomatosis in certain instances.

The condition of the generative organs was mentioned in four of the autopsies on Dercum's syndrome; in two the ovaries were atrophied, in one an ovarian cyst and hydrosalpinx were found, in one the testicles were undeveloped and showed no evidence of functional activity. Dercum's syndrome has repeatedly been observed to follow the natural menopause, and even oophorectomy, as in two cases in young women reported by Sicard and Roussy.<sup>113</sup> Similarly, all forms of adiposity and lipomatosis have been observed to follow disturbances of the generative organs, e. g., puberty, the menopause, after castration or oophorectomy. In Fröhlich's syndrome sexual infantilism (hypoplasia of the genital organs) has been emphasized as a symptom of hypophyseal tumor. Genital atrophy was found at autopsy in twelve out of thirty-two cases of "hypophyseal adiposity," collected by Marburg.<sup>115</sup> As has been shown in Group VI, genital hypoplasia and adiposity are probably also related directly or indirectly to disturbances of many of the glands of internal secretion, e. g., pituitary, pineal, thyroid, thymus, pancreas, adrenal, generative, liver.

The spleen was cirrhotic in two autopsies on Dercum's syndrome, and in both cases new-formed hemolymph glands were present in the fat deposits; in one of these cases also one of the adrenal glands was hypertrophied.

The kidneys showed marked lesions in seven of the nine autopsies on Dercum's syndrome, chronic nephritis in five and acute nephritis in two cases.

Similarly, extensive involvement of the glands of internal secretion (pituitary, thyroid, adrenal, generative, pancreas, spleen, etc.) has been demonstrated in diffuse symmetrical lipomatosis, as shown above.

These and other facts to be mentioned make it probable that the complex morbid process starts in disturbances of function or disease of

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(q) Of the physiology of the pineal gland practically nothing is known. See Dixon and Halliburton: *The Pineal Body*, *Quart. Jour. Exper. Physiol.*, Lond., 1909, ii, 283-285; and Marburg.<sup>115</sup>

these glands, one or more. See also above, under Group VI, the citation of many observations suggesting a relation of adiposity and lipomatosis to many of the glands of internal secretion.

*The Thyroid Gland.*—That disease of the thyroid is the primary and principal cause of the trophic disturbance seems highly improbable in view of the great mass of evidence that we possess relating to the physiology and pathology of this organ.<sup>(9)</sup> On the other hand, that this gland may bear some indirect relation to the process, as one of the mutually related and important glands of internal secretion, is suggested by the facts that pathological changes in the thyroid are common in Dercum's syndrome and other forms of adiposity and lipomatosis, and that thyroid medication has in many instances benefited these conditions. See Group VI.

*The Generative Glands.*—That the generative glands bear an intimate relation to the process is suggested by many facts. At puberty girls acquire the special feminine type of subcutaneous fat deposit. At the time of the menopause women frequently grow stout. Double oophorectomy is followed by distinct obesity in about 50 per cent. of women.<sup>183</sup> Dercum's syndrome has also been observed to follow oophorectomy in young women.<sup>173</sup> Eunuchs often are obese and the deposits of fat sometimes show a special distribution, as in the Skopzi.<sup>183</sup> Many of the clinical types of adiposity and lipomatosis have been observed in many instances to follow marked menstrual disturbances or the menopause.

It should be noted that the weight of evidence points to the fact that the trophic mechanism of the sexual glands resides not in the generative elements of these glands, but rather in certain interstitial cells, possibly the interstitial cells (*Zwischenzellen*) of Leydig, as Tandler and Gross<sup>183</sup> have specially emphasized in observations on animals. The functional activity of these special cells appears to determine the internal secretion of the generative glands, which in turn controls their trophic mechanism. If this view becomes accepted, it will require a new investigation of the whole problem of the trophic relations of the generative glands which is now so obscure.

Whether the relation of the generative glands to the trophic process is direct or indirect, essential or accessory to other glandular disturbance, cannot be told definitely. The general evidence, however, tends to support the view that this relation is not simple, but is involved in compli-

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(9) On the trophic relations of the thyroid gland, especially in hyperthyroidism, see Holmgren (Ueber den Einfluss der Basedow'schen Krankheit und verwandter Zustände auf das Langenwachstum nebst einigen Gesetzen der Ossifikation, Metzger & Wittig, Leipsic, 1909).

cated interrelations with other glands of internal secretion, probably in a special degree with the pituitary gland.

In the attempt to unravel the knot of problems involved in the interrelations of the generative glands and the pituitary and other glands of internal secretion to the trophic disturbances that characterize the cases under consideration, the chief point of inquiry has been to determine which of these glands, the generative or the pituitary, is the primary source of the interglandular disturbance. This problem is still undetermined, with the weight of evidence favoring the view that the primary glandular disturbance varies in different cases. Further evidence supporting this view will be presented below.

*The Pituitary Gland.*—Whether the pituitary gland initiates the process cannot be answered definitely at present. That it may do so, or at least be intimately concerned therein in certain cases, is suggested by the pathological findings in cases of Fröhlich's syndrome, Dercum's syndrome, diffuse symmetrical lipomatosis, etc. It may be said, however, that no observer, except Cushing, has yet claimed to have produced the general constitutional symptomatology described above as characterizing the several groups of abnormal fat deposit, either by grafts of the pituitary body or the administration in excess of pituitary extract (hyperpituitarism), or by partial or total hypophysectomy (hypopituitarism). Paulesco's<sup>129</sup> conclusions on this point, based on a very large number of hypophysectomies in animals performed by himself and many other experimenters, were as follows:

The hypophysis is an organ indispensable to life—its absence being rapidly fatal.

The removal of part of the cortical substance of the epithelial (anterior) lobe of the hypophysis permits the indefinite survival of the animal and causes no manifest disorder. On the contrary, the removal of all this portion of the hypophysis is equivalent to total hypophysectomy. The removal of the nervous (posterior) lobe of the hypophysis is compatible with the indefinite survival of the animal and is followed by no apparent disturbance.

Insufficiency of function of the hypophysis, resulting from total or almost total hypophysectomy, manifests no particular or characteristic symptom and, in case of prolonged survival, produces no appreciable trophic disturbance in the extremities.

Cushing<sup>24, 35</sup> alone claims to have observed any significant increase in weight (adiposity) or other important symptoms in his animals after partial hypophysectomy. His statement is as follows:

Now, it is otherwise with the anterior lobe, for its partial removal, supposedly equivalent to a condition of hypo-secretion of this part of the gland, though not incompatible with life, nevertheless leads in some cases to profound alterations—notably an increase in the deposition of fat. This condition seems to have

occurred in one of the animals of Paulesco's(*r*) series—a chance observation to which especial attention does not seem to have been paid. We have had a number of similar experiences; and indeed believe that we have succeeded in purposefully producing this condition, which we regard as characteristic of lessened secretion. The adiposity has been associated in some cases with polyuria and transient glycosuria, with shedding of hair, occasionally with unmistakable lessening of sexual activities and even with atrophy of testes and ovaries.

Perhaps the discrepancies between the results obtained by Cushing and Paulesco and others may be accounted for by the failure of the latter to devote attention to the special points that interested Cushing. At any rate, Cushing's observations, however interesting they may be, need to be presented in greater detail and to be confirmed and controlled by further work before their relation to the problem under consideration can be fairly judged.

[While proof is being corrected, Cushing's latest contribution to this subject (Crowe, Cushing and Homans: *Experimental Hypophysectomy*, Bull. Johns Hopkins Hosp., 1910, xxi, 127) has come to hand. In a series of 150 hypophysectomies on canines, "histologically corroborated," the protocols show three instances of marked increase of weight (adiposity) in adult dogs, as follows: Observation 34: partial removal of anterior lobe and stalk separation, gain in weight in six months from 14 to 24 pounds, ovaries normal, uterus infantile. Observation 54: partial removal of anterior lobe and total removal of posterior lobe, gain in weight in three and one-half months from 16 to 27 pounds, no changes in ovaries. Observation 55: partial removal of anterior lobe and total removal of posterior lobe, gain in weight in three and one-half months from 17 to 23 pounds, partial atrophy of testes. Observation 98 cannot be accepted in this connection because the dog was "young" and observation 27 because the thyroid was also removed. The three positive observations cited, while too few to warrant definite conclusions, tend to substantiate Cushing's opinion that a condition of hypopituitarism may lead to "a state of adiposity, accompanied by (or resultant to?) a secondary hypoplasia of the organs of generation" and other trophic changes, at least in certain instances.—I. P. L.]

Of the physiology of the pituitary body little is known. That it is an organ indispensable to life, the vital property residing in the anterior or epithelial lobe, has already been stated. This conclusion, however, has not been reached by all recent investigators. Gemelli,<sup>71</sup> for instance, found that complete hypophysectomy in cats produced no notable effects. Vassale and Sacchi<sup>190</sup> have been able to modify slightly the morbid

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(*r*) In Paulesco's<sup>139</sup> series the only instances of marked increase of weight in adult dogs were in Experiments lxiii (p. 234) and xix (p. 251). In one case after almost total hypophysectomy the dog survived 355 days. Four months after the operation its weight was 4,900 grams, eight months after the operation, 6,600 grams. Its weight before the operation was not stated. In the other case partial removal of the cortical layer of the epithelial lobe was performed on a dog weighing 14 kilograms. Nearly one year later the dog weighed 17 kilograms. It is easy to account for such moderate increase in weight without attributing it necessarily to hypopituitarism.

symptoms following hypophysectomy in dogs and cats by injection of pituitary extract, and Cushing<sup>34, 35</sup> has succeeded after total hypophysectomy in dogs in prolonging life "for a time, though not indefinitely, by immediate or antecedent transplantation<sup>(s)</sup> of the anterior lobe or by post-operative injection of its extract." Howell<sup>38</sup> has shown that the posterior or nervous lobe contains a blood-pressure-raising principle, and Schäfer and Herring<sup>168</sup> that the posterior lobe extract when injected into the blood causes a dilatation of the renal vessels and diuresis. Herring<sup>64</sup> has shown that this internal secretion of the posterior lobe comes probably from the epithelial cells of the pars intermedia and perhaps also from the ependymal cells of the posterior lobe.

In acromegaly and gigantism the hypophysis is almost always found altered—hypertrophy, tumor,<sup>(t)</sup> microscopic increase of the chromophile cells,<sup>(u)</sup> etc., leading many writers to the view that acromegaly and gigantism are caused by a condition of hyperpituitarism. No one has succeeded in producing symptoms of acromegaly by grafts of the hypophysis or by administration of its extract, its prolonged administration hypodermatically in growing animals producing in general no positive effect on their development, although in rare instances some retardation is noted (Caselli,<sup>24</sup> Ballet and Laignel-Lavastine<sup>9</sup>). Further, the administration of pituitary extract in the treatment of acromegaly is without apparent effect,<sup>(v)</sup> although some exceptions<sup>(w)</sup> to this rule may be admitted. On the other hand, the idea of hyperpituitarism in acromegaly receives some support from the effects of partial or subtotal hypophy-

(s) No successful transplantation of the hypophysis in man or animals has yet been reported. Complete destruction of the transplanted organ occurs within a few days or weeks.<sup>31, 34</sup>

(t) Erdheim<sup>28</sup> has reported a case of acromegaly without tumor of the hypophysis but with a tumor situated beneath the sella turcica in the sphenoid bone, composed of chromophile cells identical with those characterizing the anterior lobe of the hypophysis. The importance of this observation as a possible explanation of other instances of acromegaly in which gross and microscopic changes in the hypophysis are wanting is apparent. The location of the tumor in Erdheim's unique case is readily understood in view of Haberfeld's<sup>27</sup> studies showing that small remnants of hypophyseal tissue are constantly found at all ages at the point of origin and in the path of migration of the embryological hypophysis (anterior lobe), which arises from the buccal mucous membrane by evagination passing upward through the site of the sphenoid bone by the craniopharyngeal canal to its final position in the sella turcica.

(u) Lewis<sup>108</sup> reported a case of acromegaly in which the hypophysis appeared normal grossly but microscopically showed hyperplasia of the chromophile cells. Similar findings have since been reported.

(v) Marinesco, Mendel, Cyon, Favorski, Schultze and Joris, Witmer, Kester. Cited by Paulesco.<sup>139</sup> pp. 117-118.

(w) For example, the cases mentioned by Axenfeld, Elschmig, and Fleischer in the discussion of Ulthoff's<sup>189</sup> paper and the case of Osborne cited by Dock.<sup>153</sup>

sectomy in cases of acromegaly, definite reduction in the overgrowth of bone and soft tissue resulting (Hochenegg,<sup>64, 86, 181, 203</sup> two cases; Cushing,<sup>35, 36</sup> one case). But equally marked effects on the symptomatology have followed similar operations, i. e., excision of tumors with partial hypophysectomy, in cases of Fröhlich's syndrome, which has been represented as a condition of hypopituitarism. Hence apparently both acromegaly and Fröhlich's syndrome should be regarded as related to hyperpituitarism (or hypopituitarism) or else no valid conclusions should be based on these few cases as to the nature of the functional disturbance, whether hyperpituitarism, hypopituitarism or dyspituitarism or some other unknown process.

No hormone has yet been isolated capable of stimulating the hypophysis to permanent overactivity or pathological excess or alteration of secretion. Transplantations of the pituitary body into animals "have signally failed in this respect" (Cushing).

The pituitary body reacts to acute and chronic intoxications, e. g., pilocarpin, ichthyotoxin, diphtheria toxin, endogenous toxins, showing histological changes interpreted as augmentation or diminution of secretory activity (Guerrini<sup>74, 75</sup>).

It may be concluded, then, that, while there are weighty reasons for attributing to the hypophysis an important rôle in the etiology of the process, the available evidence does not yet justify the assumption, made by some, that the relation of the hypophysis to the process is either primary or exclusive.

#### INTERRELATION OF THE VARIOUS GLANDS OF INTERNAL SECRETION

On the other hand, there are many reasons for viewing disturbances of function of the several glands of internal secretion as interrelated and interdependent, a disturbance in one leading to secondary changes in others and in consequence a diverse symptomatology. This interrelation is shown in part by the following facts:

*Pituitary and Thyroid Glands.*—In diseases of the thyroid gland, e. g., goiter, cretinism, myxedema, cachexia strumipriva, changes in the pituitary body regularly occur, namely, hypertrophy, hyperplasia of the chromophile cells, atrophy, increase of colloid, etc.<sup>(x)</sup> Thyroidectomy causes hypertrophy of the hypophysis<sup>(y)</sup> and likewise hypophysectomy

(x) Schönemann, Comte, Pisenti and Viola, Boyce and Beadles, Burekhardt, Vassale, Coulon, Ponfick. Cited by Paulesco,<sup>139</sup> pp. 87-88.

(y) Rogowitsch, Stieda, Tizzoni and Centanni, Horsley, Eiselsberg, Lusena, Gley, Hofmeister, Leonhardt. Cited by Paulesco,<sup>139</sup> p. 88. See also Delille,<sup>41</sup> part ii, chap. x.



causes hypertrophy of the thyroid.<sup>(z)</sup> In acromegaly and gigantism the thyroid gland is usually altered, hypertrophied, atrophied, etc.,<sup>(aa)</sup> and acromegaly has been known to be complicated by exophthalmic goiter or myxedema. In Dercum's syndrome, Fröhlich's syndrome and other clinical forms of fat deposit, the thyroid gland is frequently altered and in all of these conditions the administration of thyroid extract has been followed, at least in some instances, by marked improvement in the various symptoms. Both the pituitary gland (Guerrini<sup>74</sup>) and the thyroid gland (Vincent,<sup>191</sup> Diamantberger<sup>59</sup>) react to infections and intoxications. According to Wells,<sup>199</sup> the human pituitary contains iodine<sup>(bb)</sup> in the proportion of about one to fifty of the amount contained in the thyroid.

*Pituitary and Generative Glands.*—In acromegaly and gigantism, functional or organic changes are frequently noted in the genital organs, e. g., amenorrhea, anaphrodisia, impotence, sterility, atrophy of testicles, ovaries, uterus, mammary glands.<sup>(cc)</sup> Many giants are as good as castrated in consequence of the lack of development or atrophy of the generative organs.<sup>(cc)</sup> The first symptoms of acromegaly in women may date from a previous pregnancy, and not infrequently disturbances or cessation of the menses are the earliest symptoms and may precede by many years definite signs of acromegaly.<sup>153</sup> The elongation of the legs and the abnormal epiphyseal development, which characterize gigantism, are observed also in castrated men<sup>(dd)</sup> and animals.<sup>(ee)</sup> In eunuchs<sup>183</sup> enlargement of the sella turcica has been observed. Fichera<sup>65</sup> found excision of the testicles or ovaries in animals regularly followed by

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(z) Cushing,<sup>35</sup> p. 252.

(aa) Hinsdale, Fournival, Lancereaux, Murray, Launois and Roy, Bassoe. Cited by Paulesco,<sup>139</sup> p. 88.

(bb) Schnitzler<sup>109</sup> also found iodine in the human pituitary, but Baumann<sup>12</sup> in the human and Halliburton, Candler and Sikes<sup>79</sup> in the human and the bovine pituitary failed to find iodine.

[Since the foregoing was written, Wells (The Presence of Iodine in the Human Pituitary Gland, Jour. Biol. Chem., 1910, vii, 259) has recorded new observations on this subject. He found traces of iodine in the pituitary glands of three patients who had received iodids before death, but was unable to demonstrate iodine in the pituitary glands of twenty-two patients who had not received iodine before death. He therefore concludes that the presence of iodine as a normal constituent of the human pituitary gland must be regarded as still unproved. Simpson and Hunter (Proc. Soc. Exper. Biol. and Med., 1909, vii, 11) were also unable to demonstrate iodine in the pituitary glands of thyroidectomized sheep.]

(cc) Paulesco,<sup>139</sup> p. 116.

(dd) Lortet, Ecker, Becker, Godard, Pittard, Poncet, Sellheim, Briau, Pirsche. Cited by Paulesco,<sup>139</sup> p. 116. Also Tandler and Gross,<sup>133</sup>

(ee) Fichera. Cited by Paulesco,<sup>139</sup> p. 117.

changes in the pituitary body, i. e., hypertrophy, hyperplasia of the chromophile cells, congestion, etc. Subcutaneous injections of testicular extract in castrated cocks caused the pituitary body to resume the normal type found in uncastrated cocks, this modification disappearing promptly when the injections were stopped. Several observers have noted characteristic changes in the pituitary body during pregnancy both in women<sup>(ff)</sup> and animals.<sup>(gg)</sup> In Fröhlich's syndrome pathological changes in the hypophysis may be accompanied by sexual infantilism. Similarly, autopsies in cases of Dercum's syndrome show changes in the pituitary body and in some instances atrophy of the ovaries or testicles; furthermore, Dercum's syndrome, as well as all forms of adiposity and lipomatosis, are frequently associated with or follow on changes of function of the generative glands, i. e., menopause, oophorectomy, etc.

*Pituitary and Adrenal Glands.*—There is an intimate physiological relation between the pituitary and adrenal glands, evidenced by many facts. The chromaffin tissue that seems especially to characterize the adrenals is found also in the hypophysis (Wiesel). Both glands contain a blood-pressure-raising principle (Howell). Both react to infections and intoxications. Adrenalin glycosuria is well known (Blum, Herter), and glycosuria frequently occurs in affections of the hypophysis, e. g., acromegaly, tumors, partial or total hypophysectomy. Pigmentation of the skin, characteristic of Addison's disease, occurs commonly in acromegaly (Brooks), has been observed in a case of traumatic destruction of the hypophysis (Wasdin), and not infrequently in Dercum's syndrome and other clinical forms of adiposity and lipomatosis. Acromegaly is characterized by overgrowth of certain structures and similarly adrenal tumors have been known to be associated with excessive development of the genitals, hair and fat [Woolley, Bullock and Sequira<sup>(hh)</sup>]. Hypertrophy of the hypophysis was observed in a case of Addison's disease by Pansini and Benenati<sup>(hh)</sup> and likewise has been found after adrenalectomy in some instances by Boinet,<sup>(ii)</sup> Marengi<sup>(ii)</sup> and others. In acromegaly the adrenals are sometimes atrophied (Dock) and in one case of Dercum's syndrome adrenal hypertrophy has been noted.

*Pituitary and All the Glands of Internal Secretion.*—Cushing<sup>35</sup> says: "It is impossible to remove—probably partially to remove—the hypo-

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(ff) Comte, Launois and Mulon, Morandi. Cited by Paulesco,<sup>139</sup> p. 117; also Erdheim and Stumme.<sup>60</sup>

(gg) Guerrini, Morandi. Cited by Paulesco,<sup>139</sup> p. 117.

(hh) Cited by Dock,<sup>53</sup> p. 359.

(ii) Cited by Paulesco,<sup>139</sup> p. 89.

physis without producing marked alterations in all the other glands—thyroid, parathyroid, adrenal, testicle, ovaries, islands of Langerhans, and thymus,” and likewise the reverse is probably true. <sup>(jj)</sup>

#### MUTUAL RELATIONS BETWEEN MANY OF THE GLANDS OF INTERNAL SECRETION

In addition to the above facts showing especially relations existing between the pituitary and the thyroid, generative and adrenal glands, a still wider interrelation of the glands of internal secretion is indicated in part by the following facts:

The adrenals are known to have close relations with many other glands of internal secretion. This has already been shown for the pituitary gland. Eppinger, Falta and Rudinger<sup>57</sup> have conclusively demonstrated intimate mutual relations between the adrenals (chromaffin system), pancreas and thyroid,<sup>(kk)</sup> which may be summarized as follows: (a) the thyroid and pancreas inhibit the action of each other; (b) the pancreas and chromaffin system inhibit the action of each other; (c) the thyroid and the chromaffin system increase the action of each other. In Addison's disease there may be persistent thymus, hypertrophied spleen and atrophied thyroid. Hypoplasia of the adrenals and of the entire chromaffin system may occur in status thymicus (Dock, Hedinger). Hart<sup>(ll)</sup> found the adrenals enlarged in animals injected with the juice of a persistent thymus. Relations between the adrenals and generative glands is suggested by the occurrence of pigmentation of the skin in many ovarian and uterine disorders and by the facts that in osteomalacia the adrenals have been found hyperplastic in some instances and either oophorectomy or the administration of adrenalin (Bossi and others) has been found to benefit the condition in some cases. In osteomalacia a relation to the thyroid also is indicated by the frequent complication of simple goiter and even in some instances of exophthalmic goiter. The pigmentation of the skin that is frequently noted in many conditions having known or supposed relations with certain glands of internal secretion, e. g., acromegaly, exophthalmic goiter, myxedema, Dercum's syndrome, adiposity and lipomatosis, von Recklinghausen's neurofibromatosis, arthritis deformans, bronzed diabetes, uterine and ovarian affections, etc., suggests a possible relation to the adrenal glands or to the chromaffin system in general.

(jj) Delille,<sup>41</sup> part 2, chap. x: Perrier: Contribution à l'étude des réactions de Phypophyse à la suite d'ablations glandulaires. 1909, Paris, H. Paulin & Cie.

(kk) Confirmed by Grey and Sautelle,<sup>52</sup> King,<sup>55</sup> McCurdy.<sup>121</sup>

(ll) Cited by Dock,<sup>53</sup> p. 355.

The relation of the thyroid to the generative glands is shown by the common occurrence of hypertrophy of the thyroid with puberty, menstruation, pregnancy, lactation, etc. In pregnancy the pituitary, thyroid and adrenals are all hypertrophied, as a rule.<sup>(mm)</sup>

Very intimate relations are well known to exist between the thyroid and parathyroid glands. Both these glands contain iodine and removal of one is usually followed by changes in the other.

Many facts suggest the relation of the thymus to the other glands of internal secretion. Some of these have been pointed out. "The thymus gland is in a state of evolution until the age of puberty. It then undergoes regressive changes, at first abruptly, later more gradually. It is, in all probability, a functional organ throughout life" (Pappenheimer<sup>138</sup>). Castration causes delay of involution of the thymus (Henderson) and excision of the thymus causes accelerated development of the testes (Paton). In status lymphaticus the thymus is almost always hyperplastic, the thyroid usually shows colloid hyperplasia, the genital organs are often hypoplastic (Bartel<sup>10</sup>). Changes in the thymus occur commonly in many affections of the ductless glands, e. g., goiter, exophthalmic goiter, myxedema, cretinism, acromegaly, Addison's disease, etc. (Warthin,<sup>196</sup> Pappenheimer<sup>138</sup>). Like many of the other ductless glands, the thymus reacts characteristically to acute and chronic infections and intoxications (Pappenheimer.<sup>138</sup>).

Relations between the spleen and pancreas have been established by Schiff, Herzen and others,<sup>(nn)</sup> who have shown that the spleen furnishes to the blood an internal secretion that is capable of activating the pancreatic zymogen into trypsin.

Tigerstedt and Bergman<sup>187</sup> and others<sup>13, 144</sup> have demonstrated that the kidney produces a blood-pressure-raising principle, and Pi y Suñer<sup>147</sup> and others assert that the kidney produces also an internal secretion that is concerned in general metabolism, the absence of which after nephrectomy causes uremia. There are other reasons for thinking that the kidney may belong to the system of glands of internal secretion and this relation may perhaps have an important bearing on the etiology of the chronic nephritis that occurs frequently in acromegaly, myxedema, Dercum's syndrome, etc.

Many of the glands of internal secretion, e. g., thyroid, ovary, testicle, adrenal, pituitary, when administered to animals, stimulate the oxygenation of the tissues.

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(mm) Guerrini, Morandi, Comte, Launois and Mulon. Cited by Paulesco,<sup>122</sup> p. 117.

(nn) Cited by Lyon,<sup>111</sup> p. 737.

In acromegaly the hypophysis and the thyroid are almost always abnormal; the generative glands are often hypoplastic or degenerated; the thymus is often persistent or enlarged; the kidneys are often cirrhotic; the adrenals and pancreas are sometimes cirrhotic; and the parathyroids, pineal gland and spleen are sometimes hypertrophied (Dock). Acromegaly is sometimes complicated by exophthalmic goiter, myxedema, diabetes, epilepsy, adiposis, lipomatosis, etc.

The above facts are sufficient to indicate the complexity of the problem to be solved in determining the relations of the different glands of internal secretion to the pathological process involved in adiposity and lipomatosis. That such relations exist is evident. What they are is beyond our ability to understand at present. To argue from the presence of pathological changes in one of these glands or from the benefit resulting from the administration of a glandular extract that the corresponding gland is specifically and exclusively related to the etiology of the morbid process is hazardous and not based on a comprehensive conception of the intricate mutual relations existing between many of these glands. Is the hypophysis essentially and are the other glands only secondarily or indirectly concerned? Is the varying symptomatology of the process, as exhibited by the several clinical groups, as well as within each of these groups, dependent on variations in the degree of involvement of these different glands? If so, what determines the unequal involvement? Can primary disturbances in any one of these different glands initiate the morbid process? To all such questions we must answer: *Ignoramus*. Our knowledge of the trophic relations of these glands is fragmentary and consists mostly of "guesses and gaps," as Foster said of our knowledge of metabolism in general. We must await future investigation for elucidation of these, the deepest secrets of biological chemistry. But in taking this conservative stand let us not blind our eyes to possibilities and refuse to be interested in any working hypothesis, however partial it may be, that can help to encourage investigation and thus ultimately to establish the truth.

It may be earnestly hoped that investigation may be advanced by the exact report of the clinical and pathological findings in a larger number of cases of abnormal fat deposit, whether they conform to some type or syndrome picture or not. Irregular and atypical cases ought especially to be studied and reported, as they will surely be found to throw light on the nature of other cases that conform to one of the several varieties heretofore generally represented as typical or constituting distinct disease entities. In autopsies the hypophysis and other glands of internal secretion should be examined not only grossly but also microscopically

and by a pathologist familiar with the physiological and pathological variations in these glands. Especially does this apply to the hypophysis, whose cellular variations are at present so little understood that it is impossible to interpret them. This fact is aptly expressed by Cushing in the statement: "There are no *normal* pituitary glands."

In this connection it may be pointed out that multiple neurofibromatosis (von Recklinghausen's disease) shows many and striking analogies in its symptomatology to the process of abnormal fat deposit and possibly will be found to be closely related etiologically to this process. Multiple neurofibromatosis<sup>81, 150, 152, 154</sup> is characterized by the wide dissemination over the body and in some instances within the central nervous system of fibromata arising from proliferation of the connective tissue of the peripheral nerves or of the central nervous system. The tumors are usually painless, but pain, both spontaneous and induced by pressure in the tumors, may be a feature in certain cases. Constitutional symptoms may be exhibited, including various psychic, nervous, motor, vasomotor, sensory and trophic disorders. Heredity plays a distinct part, about 20 per cent. of cases occurring as a family disease, sometimes including several generations. A study of the possible relations of this disease to the important glands of internal secretion might prove profitable, and throw light on the same problem in the process of abnormal fat deposit.

And finally it may be suggested that the subcutaneous fibroid nodules of inflammatory rheumatism and certain rheumatoid affections may be symptomatic of disturbed function of the hypophysis, thyroid or other glands of internal secretion. This possibility is suggested by the facts that these nodules are sometimes distinctly lipomatous (as in the second group of Fletcher's<sup>69</sup> classification), sometimes painful; that rheumatoid symptoms frequently characterize all classes of abnormal fat deposit; that arthritis in certain forms may be at least partially related, etiologically, to disturbances of function of the thyroid gland and can be benefited by thyroid medication (Diamantberger<sup>50</sup> and others), and that toxic agents are capable of producing changes in the functional cells of the hypophysis, thyroid and adrenal glands.

*Treatment.*—Enough has already been said to indicate our therapeutic poverty in these cases. Perhaps the future may have in store for us a potent and scientific therapy derived from the pituitary or other glands of internal secretion. The indications of etiological relation between functional derangement or disease of these glands and the pathological process under consideration justify their experimental use. In the absence of a more promising glandular therapy, thyroid may be tried. In many instances its use continued for many months has been followed by

amelioration of symptoms, not only in cases presenting more or less of Dercum's syndrome, but as well in cases belonging to the other clinical groups. Its beneficial effects may perhaps depend on a secondary activation (or depression) of other glands of internal secretion, e. g., pituitary, generative, as many have suggested. Its administration and dosage ought to be regulated carefully for each case, as its indiscriminate use is dangerous. In general, small doses (one-quarter to one-half of a grain of the desiccated gland daily) should be first employed and the dosage gradually increased and always kept well within the limit of tolerance. It is also advantageous to suspend the use of the drug one out of every four weeks when it is used over a long period. The desiccated substance or extract of the separate lobes, especially the anterior lobe, of the pituitary body<sup>(oo)</sup> should receive a thorough clinical trial. Cases presenting definite signs of tumor of the hypophysis have already proved amenable to relief by surgical measures, either excision of the tumor with partial hypophysectomy or simple incision of the dural investment of the hypophysis, the latter procedure, however, effecting only relief from the intractable headache by removal of its usual cause, i. e., distention of the dural pocket enclosing the gland (Cushing). The clear relief from distressing tenderness and pain of the fatty deposits following profuse hemorrhage in two of the cases above reported (Cases 2 and 3) suggests the therapeutic use of free bleeding in suitable cases. Other symptomatic remedies have already been mentioned and will suggest themselves according to the special indications encountered.

#### CONCLUSIONS

In brief, the following facts and conclusions may be stated:

1. A series of twenty personal observations, embracing a wide variety of cases, is recorded.

2. The following clinical groups of fatty deposit are considered: (1) Dercum's syndrome ("adiposis dolorosa"); (2) simple adiposity or obesity; (3) nodular circumscribed lipomatosis, solitary, multiple or symmetrical; (4) diffuse symmetrical lipomatosis, including "fatneck" (Madelung); (5) neuropathic edema, pseudo-edema, pseudolipoma, lipoma; (6) "adipositas cerebialis," including Fröhlich's syndrome.

3. These several clinical groups are compared with one another and especially with Dercum's syndrome, *adiposis dolorosa*, in reference to their clinical symptomatology, constitutional relations, pathology, etiology and treatment. In these respects they are thought to be not only

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(oo) Commercial preparations of the separate lobes of the pituitary body are now available from American manufacturers.

closely related, but essentially identical, being only variations of a common morbid process. They do not constitute clearly defined entities, but rather varieties, phases, or case-groups of a common morbid process. They often blend with one another and exhibit common features, so that individual cases cannot be exactly classified in any single group.

4. Dercum's syndrome characterizes certain cases selected from all groups and is not a clinical or pathological entity.

5. Fröhlich's syndrome is not an entity, but merely a grouping of special symptoms in selected cases of hypophyseal tumor.

6. Diffuse symmetrical lipomatosis, including *Fetthals* (Madelung), or *adéno-lipomatose symétrique à prédominance cervicale* (Launois and Bensaude), is shown to have no special pathogenic relations with lymphatic tissues, and the designation, adenolipomatosis, applied by Launois and Bensaude and most subsequent writers, is consequently unjustified and should be abandoned. The symptomatology is that of the other groups, some cases showing the full picture of Dercum's syndrome.

7. Nodular, circumscribed, encapsulated lipomatosis, whether solitary, multiple or symmetrical, is characterized chiefly by the discreteness of the fatty deposits and the investment of connective tissue. These features determine only a variety, shared partly by cases belonging to other groups. The general symptomatology is similar to that of the other groups, many cases agreeing in all respects with Dercum's syndrome.

8. Neuropathic edema, pseudo-edema, pseudolipoma and lipoma have been described chiefly by French writers, who represent them as stages of evolution in a common morbid process. Their symptomatology is that common to all groups. Some of the cases agree essentially with Dercum's syndrome. They are poorly classified and probably represent only variations.

9. All the groups show a strong tendency to be characterized by constitutional symptoms embracing a wide variety. It is out of these symptoms that certain ones have been selected and attributed to certain syndrome-case-groups. But the same symptoms in every possible variation and combination are common to all the groups.

10. These symptoms include especially many psychic, sensory, motor, vasomotor, secretory and trophic manifestations.

11. Special attention is called to various arthralgic and arthritic and neuralgic and neuritic manifestations as belonging to the constitutional symptomatology of the morbid process.

12. The etiology of the process, thus broadly considered, is unknown. Only two views, connecting the process with disturbances of the nervous system or of the glands of internal secretion, seem broad enough to har-



monize with all the facts. These two views are not necessarily opposed, but can be resolved into one, by assuming that the nervous system is secondarily disturbed by primary disturbances in the glands of internal secretion, or *vice versa*.

13. The pathological findings and the general evidence suggest the view that the process is related to alterations in the glands of internal secretion. Many of these glands have been found altered.

14. Special importance has been attached by many writers to the pituitary gland in the pathogenesis, and the evidence tends strongly to support this view, but the facts at present known do not justify the assumption that this gland is exclusively concerned in the process.

15. The complex mutual relations between all of these glands are considered and the view suggested that one or more or all of them may be concerned in the pathogenesis, and that the variation in the symptomatology of the different groups and cases may depend on the varying degree of involvement of these several glands and the nervous system.

16. Heredity as a factor in the etiology is pointed out and the cases exhibiting this relation are reviewed.

17. The treatment is unsatisfactory. Thyroid preparations have given the best results. Other forms of glandular therapy should be tried.

In conclusion, I take pleasure in acknowledging my grateful appreciation of the kind interest and valuable assistance of Dr. Grover W. Wende in the study of several of the personal observations recorded.

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THE CONTROL OF TYPHOID FEVER IN CITY AND COUNTRY  
WITH A DESCRIPTION OF A MODIFIED HESSE'S MEDIUM FOR THE DETECTION  
OF THE TYPHOID BACILLUS IN EXCRETA AND FLUID FOODS\*

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Before describing the various methods for the control of the spread of typhoid fever and the assistance rendered to these measures by means of a modified Hesse's medium, we shall first describe the manufacture of this medium and its uses and limitations in the detection of the typhoid bacillus.

MANUFACTURE OF MEDIUM

Jackson<sup>1</sup> in his article describes very thoroughly the evolution of a differential medium for the typhoid bacillus but as the latest medium seems to be the most successful, we shall simply describe Hesse's semi-fluid medium, including our own modification, quoting from the aforementioned article in a somewhat condensed manner.

The formula of the medium is as follows:

Agar (dried at 105 C. for half an hour)	4.5 gm.
Liebig's extract of beef	5 gm.
Peptone (Witter)	10 gm.
Sodium chlorid	8.5 gm.
Distilled water	1000 c.c.

Before using, the agar should be dried at 105 C. for half an hour to free it from all moisture. This medium should be kept in an ice-chest, the air of which is artificially provided with moisture.

The agar is dissolved in 500 c.c. of distilled water by heating and the loss by evaporation is made up. The peptone, beef extract, and salt are dissolved in another vessel containing 500 c.c. of distilled water and the loss of weight by evaporation is made up by the addition of distilled water. The two solutions are then mixed and boiled for thirty minutes, the loss of weight being again made up by the further addition of distilled water. It is next filtered, the reaction corrected to 1 per cent. normal acid, and 10 c.c. are placed in each test-tube. It is then autoclaved at 15 pounds pressure for twenty minutes and stored in the ice-box.

\* From the Bacteriological Laboratory of the State and City Boards of Health, Baltimore, Md. Read at the Thirty-seventh Annual Meeting of the American Public Health Association, Richmond, Va., October, 1909.

1. Jackson and Melia: Jour. Infect. Dis., 1909, vi, 194.

## METHOD OF DILUTION EMPLOYED

One gram of feces, or 1 c.c. of urine, or of a bile culture of urine, feces, milk, or water is added to 9 c.c. of sterile water. From Tube No. 1, 1 c.c. is poured into a plate, a second c.c. is inoculated into tube or water-blank No. 2. From Tube No. 2, 1 c.c. is poured into Plate No. 2, and 1 c.c. is placed in Tube No. 3, and this is continued through eight water-blanks and plates.

We have found the above technic serviceable in detecting the presence of the typhoid bacillus in water and other fluid foods, but in making examinations of the urine and feces even the last plates are so crowded that we have adopted the loop method for making cultures from the urine and feces. One loopful of feces or 1 c.c. of urine is placed in a water-blank containing 10 c.c. One loopful from this water-blank is transferred into melted agar Tube No. 1, and one loopful is transferred from melted agar No. 1 into melted agar No. 2. This method of dilution is employed through a series of ten melted agar-tubes, but in the last five melted tubes two loopfuls instead of one are used each time for inoculating the melted semisolid agar. By this method only a few large characteristic colonies will appear in the later dilutions, from about the sixth to the tenth plate made from the tubes. These colonies are well separated, and there is no danger of obtaining a mixed culture.

On plates in which the colonies are few in number the typhoid bacillus presents a characteristic appearance. On such plates the colonies of the *Bacillus typhosus* are much larger than those of the *B. coli*, often measuring several centimeters in diameter. They have an opaque nucleus surrounded by a translucent area, beyond which is a circular white edge which presents a concentric arrangement. The colon bacillus, on the other hand, occurs as a white colony seldom larger than the head of a pin.

By the use of this medium Hesse<sup>2</sup> has been able to isolate the *B. typhosus* from stools and urine, while Jackson<sup>1</sup> has also obtained it from milk artificially infected with small numbers of the organisms, from the Hudson River, and small water-supplies. Since the typical appearance of the typhoid colony on semi-fluid agar is dependent on its active motility, it is not surprising that the *B. paratyphosus*, *B. fluorescens liquefaciens* and even very motile *B. coli* simulate closely the colonies of the *B. typhosus*, as mentioned by Jackson. Although the colonies of these bacilli generally do not present the translucent zone between the center and periphery, yet not infrequently they cannot be differentiated from typical typhoid colonies.

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2. Hesse: Centralbl. f. Bakteriol., 1908, xlvii, 89; Ztschr. f. Hyg., 1908, lviii, 441.

## MODIFICATION

In using this Hesse's medium for the detection of the typhoid bacillus in feces, urine, blood-cultures, oysters, and water, we often encountered the same difficulty in distinguishing between colonies of typhoid bacilli and other motile organisms, and our difficulties were even increased by means of colonies of the *B. alkaligenes*. We were often compelled to fish many colonies, to run them through culture material, and to test them with immune typhoid serum before we could distinguish between the typhoid bacillus and other motile organisms.

One of us had noted that the typhoid bacillus would readily acidulate ordinary nutrient agar to which 1 per cent. of lactose and 5 per cent. of glycerin had been added. We determined to apply this observation to the detection of the typhoid bacillus, and after many experiments we have found that the most satisfactory semisolid medium can be prepared by adding 6 instead of 4.5 gm. of agar, and by also adding 1 per cent. of lactose and 5 per cent. of glycerin. The larger quantity of agar is added since glycerin always increases the fluidity of a medium. A most important point is to color the medium by means of a 1 per cent. solution of azolitmin powder dissolved in boiling water after the reaction has been corrected to the neutral point. This medium is then used as a plate culture for water, feces, oysters, blood cultures, and urine. In plating out stools and urine much time is saved, as the *B. alkaligenes* forms a typical blue colony while that of the typhoid bacillus is red. Both of these colonies show the typical concentric zone. The colon bacillus is almost always small, concentrated, and forms a superficial moist red colony which bears no resemblance whatever to the much larger spreading typhoid colony. We have occasionally met motile *B. coli* in colonies resembling those of typhoid, and these can be distinguished from the typhoid bacillus only by the usual cultural tests. The other motile organisms, such as the *B. proteus*, *B. fluorescens liquefaciens*, and the *B. pyocyaneus* are almost always alkaline, and the colonies are therefore blue, but the paratyphoid bacillus forms a red colony with a concentric zone, and can be distinguished from the typhoid bacillus only by cultural tests and the use of immune serum. In making a diagnosis, therefore, we have inoculated typical red colonies into Dunham's solution, incubated them for twenty-four hours and then tested them for agglutination with typhoid immune serum, furnished by Parke, Davis & Co., which will agglutinate the typhoid bacillus at a dilution of 1 to 100,000. We have found a dilution of 1 to 5,000 to be perfectly safe in differentiating between the typhoid bacillus and the other organisms mentioned above, since we have frequently tested all of these organisms with this dilution

with negative results. If the agglutination test is negative, we inoculate the subculture into glucose, lactose, and saccharose fermentation tubes, milk, and gelatin, and decolorize by Gram's method. We also test its agglutination with alpha and beta paratyphoid immune agglutinative serum, kindly furnished by Dr. J. J. Kinyoun, of Washington, D. C. It is also important to inoculate potato, and the differences in these various media enable us to recognize the paratyphoid bacillus or any other of the various types mentioned above. There is one source of difficulty, however, which we have been unable to eliminate, namely, the presence of the *B. subtilis*. This organism forms pink acid colonies with concentric zones. The colonies are usually much larger than the typhoid colonies, often measuring from 3 to 5 cm. in diameter, and they can be immediately distinguished by staining by Gram's method. As a routine procedure, therefore, we have adopted the plan of placing a ring around the outside of a plate below each colony which we intend to fish, and numbering these rings. Each colony is then subjected to Gram's method of staining, and we only select pink, concentric, Gram-negative colonies for further study. To recapitulate: Acid, concentric colonies are ringed, numbered, and subjected to Gram's stain before further study. If they decolorize by this method, they are inoculated into Dunham's solution. In twenty-four hours they are subjected to the agglutination test with an immune serum at a dilution of 1 to 5,000. If they agglutinate, they can be absolutely proved by inoculating the culture materials mentioned above, and if they fail to agglutinate with immune typhoid serum, the cultural tests and paratyphoid agglutinative test will usually prove them to be the *B. paratyphosus*, but very rarely they turn out to be motile colon bacilli or the *B. proteus*.

#### STUDIES IN WATER-BORNE TYPHOID

We have made use of our modified Hesse's medium in the study of the subject of water-borne typhoid in both Baltimore and the rural districts of Maryland, but before describing our results it is necessary to refer to the work of Jackson<sup>3</sup> in his study of the seasonal distribution of typhoid fever in large cities. In his Chart 3 he shows the average monthly variation in the typhoid fever death-rate of three types of cities. Type 1 includes Dresden, Vienna, and Munich, which have good water-supplies and sewage disposal and excellent sanitary conditions. These have a uniformly low typhoid death-rate regardless of temperature, the yearly typhoid death-rate never rising so high as 10 per hundred thousand. Type 2 includes Baltimore, Boston, and New York, cities having fairly

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3. Jackson: Report to Merchants' Association of New York, April, 1909.

good water-supplies, but at times of charting comparatively poor sewage disposal or bad general sanitary conditions, allowing the transmission of disease by flies and a monthly typhoid death-rate following the temperature. Type 3 includes Cincinnati, Chicago, and Philadelphia, cities having at the time of charting poor water-supplies and uniformly high typhoid death-rates throughout the year with little regard to temperature.

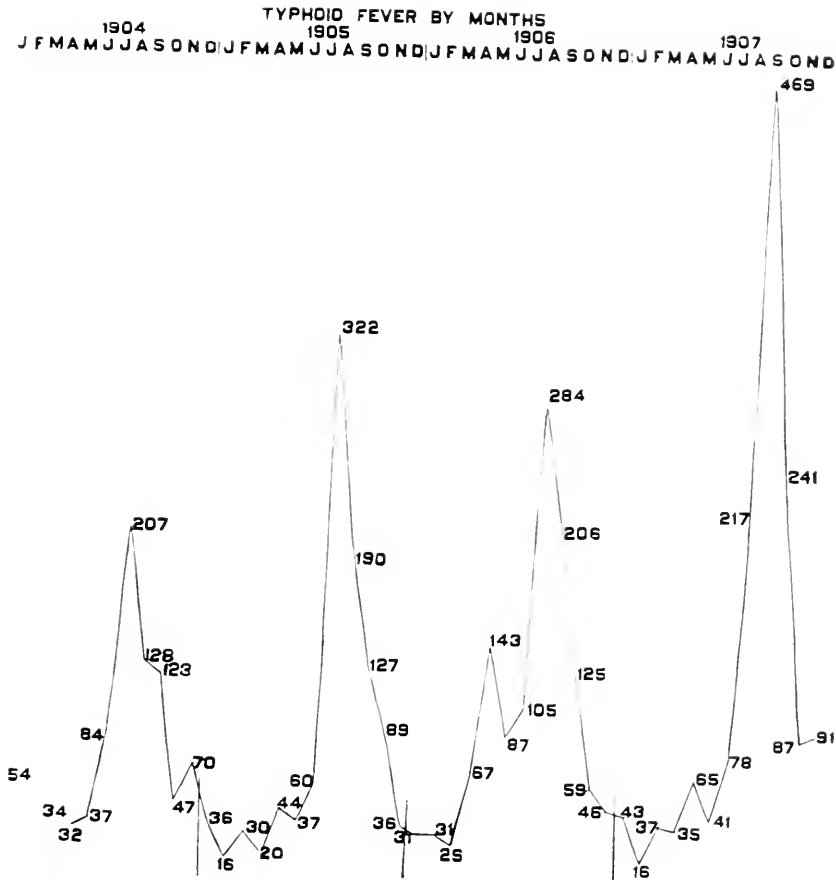


Fig. 1.—This chart shows the typical seasonal rise in the cases of typhoid fever during the months of July, August and September, when the flies are most prevalent. The 143 cases during May, 1906, are portions of a milk epidemic.

In Type 2 the monthly death-rate runs along between 1 and 2 until about June 1, and in Boston until July 1. It then begins to rise, reaching its highest point (or 3) in New York, and its highest (or 6) in Baltimore about the first of September. In Boston it reaches its highest point (or

5.5), about October 1. The death-rates then all steadily decline, reaching their uniform point below 3 about January 1. This seasonal distribution about corresponds to the fly season, and Jackson<sup>3</sup> by an ingenious set of experiments has shown that flies will increase from two on June 1 to 6,224 in the height of the fly and typhoid season, about August 1. He believes that in such cities the flies transmit typhoid bacilli from cess-pits and surface privies to the foods in kitchens and dining rooms, and thinks that by destroying the larvæ and breeding-places of the flies and by keeping the adult flies out of houses by means of screens, typhoid fever can be greatly reduced. In Type 3 there is no especial increase during the fly season, since the monthly typhoid death-rate is uniformly high throughout the year. These cities were properly sewered and the fly was unable to feed on typhoid dejecta. The water-supplies were polluted and most of the typhoid fever can be attributed to the drinking-water in these cities.

In the study by Jones<sup>4</sup> of the seasonal distribution of typhoid fever in Baltimore the charts following page 72 show the rise during the fly season in a striking manner, and as there are some 90,000 cess-pits in the city and a number of surface privies in the annex, the results correspond with Jackson's findings very closely. In all such studies, however, the absence of the typhoid bacillus in the water-supply should be proved by a large number of experiments, and we have carried out some investigations along this line.

We first studied over 500 colonies of organisms obtained from the city tap. These simply consisted of blue colonies in lactose-litmus agar and Conradi's agar-plate cultures. We never isolated a typical typhoid organism by this method, but these older methods are hardly fit for detecting typhoid bacilli in water. Within the last year, however, we have been obtaining specimens from one of the two collecting reservoirs of Baltimore. These specimens have been obtained from the bottom of the lake either at the entrance of the supply, or at the dam at the other end. The depth of our soundings ranged from 12 to 25 feet, and we have centrifugalized 100 c.c., incubating the sediment in 10 c.c. of lactose bile for twenty-four hours, as recommended by Jackson for water investigations. We have studied about 250 colonies, but have isolated the typhoid bacillus in only two instances, as most of our colonies proved to be a chromogenic organism, the *B. auranticus*, or in earlier investigations the *B. alkaligenes*, the *B. fluorescens liquefaciens*, or the *B. proteus*, as at this time we used uncolored Hesse's medium.

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4. Jones: Ann. Rep. Health Dept. Baltimore, 1907, p. 44.

The various methods used for the isolation of the typhoid bacillus from drinking-water have been thoroughly described by Willson.<sup>5</sup> These methods are filtration, chemical precipitation, serum agglutination, methods of enrichment, apparatus depending on the more active motility of the typhoid bacillus, and the use of solid or semisolid media in plate cultures.



Fig. 2.—This map for 1907 shows a large number of cases distributed evenly throughout the city. Many of these cases were probably caused by infected water, but it is hard to separate the cases caused by water-borne infection from those caused by flies.

In a careful examination of the literature he was able to find only six authentic cases in which a typical typhoid bacillus confirmed by agglutination experiments was isolated from a water-supply. We would add a seventh case in the isolation of the organism from the Mississippi River

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5. Willson: Jour. Hyg., 1905, v. 429.

at Minneapolis, by Wesbrook and Willson. This, however, is not accepted as an authentic case by Willson, since the Pfeiffer reaction was not carried out. The microscopic agglutinative tests were, however, carefully performed, and we believe that this case should be included among the well-authenticated cases. As mentioned above, Jackson has isolated the typhoid bacillus from the Hudson River and from small water supplies, such as streams and wells.

#### DESCRIPTION OF TYPHOID BACILLI ISOLATED FROM THE GENERAL WATER-SUPPLY

In October, 1909, we obtained a sample of 150 c.c. of water from Lake Roland, one of the two principal impounding reservoirs. The water from this lake is led by a conduit  $3\frac{1}{4}$  miles in length into a reservoir, and a second conduit 1 mile in length leads a portion of this water into a second reservoir near the center of the city. The water from this source is distributed to a large part of the northern annex of the city and to about one-third of the city proper in its central portion.

This water was centrifugalized and the sediment was inoculated into 10 c.c. of lactose bile. This was incubated for twenty-four hours and a series of plates was then made in our modified Hesse's medium in the manner described above. A number of colonies appeared in plates which were red, large and concentric, and pure cultures from two of these colonies gave the following characteristics:

In their morphology the bacilli were short with rounded ends; they decolorized by Gram's method. They were actively motile and gave all the cultural characteristics of the typhoid bacillus, failing to ferment glucose, lactose, and saccharose, failing to produce indol or to liquefy gelatin, faintly acidulating litmus milk, acidulating glycerin-lactose-litmus agar, and producing a barely visible moisture on potato.

#### AGGLUTINATIVE REACTIONS WITH POSITIVE TYPHOID BLOOD

Tests were made from cultures in peptone solution with known typhoid blood which produced a positive Widal reaction with the laboratory typhoid at a dilution of 1 to 50. This blood in the same dilution when mixed with the twenty-four hour peptone solution cultures of the typhoid bacilli isolated from water gave a positive Widal reaction at the end of two hours. Since the isolation of these organisms about three months ago we have tested them with seven other specimens of known typhoid blood, which gave a positive reaction with our laboratory typhoid at a dilution of 1 to 50. The same specimens of blood gave a positive reaction with our water-typhoid organism at a dilution of 1 to 50. We also tested



these organisms with an immune serum made by injecting a rabbit with gradually increasing non-fatal doses of a typhoid bacillus isolated from a well which produced an outbreak of typhoid fever in a boarding school. This immune serum agglutinated our laboratory typhoid at this time at a dilution of 1 to 100, having lost some of its potency. It also agglutinated the water typhoid organisms at the same dilution. The only negative test we obtained was with a typhoid immune serum furnished by Parke, Davis & Co., which agglutinated our laboratory typhoid bacillus at a dilution of 1 to 100,000. This same serum, however, would agglutinate six other strains of typhoid bacilli obtained from cases only at a dilution varying from 1 to 10,000 to 1 to 5,000. We also isolated several strains of typhoid bacilli from a case of enteric fever, which would not agglutinate with this serum even at a dilution of 1 to 1,000, and these water organisms are also negative with this serum at the same dilution. We obtained another agglutinative serum from Dr. J. J. Kinyoun, which agglutinated an organism obtained from typhoid fever at a dilution of 1 to 1,000. The same serum agglutinated one of the water organisms mentioned above at a dilution of 1 to 50.

*Pathogenesis.*—Two guinea-pigs were inoculated intraperitoneally with the washings of a twenty-four-hour culture on a slanted blood-serum surface  $2\frac{1}{2}$  inches in length. The animals died in from eighteen to twenty-four hours with purulent peritonitis and bacteriemia, the bacilli being isolated from the peritoneum and various viscera.

#### TYPHOID BACILLI ISOLATED FROM A TRIBUTARY OF LAKE ROLAND

We also isolated two typical organisms from a stream which passes through a suburban town about 2 miles from the above-mentioned lake. The stream receives considerable sewage from this town and the specimen was obtained from the stream just before it enters the lake.

These two organisms resembled exactly in their morphology, cultural reaction and pathogenesis the specimens described above. They failed to agglutinate with the typhoid immune serum furnished by Parke, Davis & Co., which at the time of these experiments had a maximum dilution of 1 to 25,000, at a dilution of 1 to 1,000. Each of these organisms gave positive reactions with four known typhoid bloods, and also agglutinated at a dilution of 1 to 50 and 1 to 250, respectively, with the Kinyoun immune serum, which agglutinated bacilli isolated from typhoid fever cases at a dilution of 1 to 1,000.

Later experiments show that the former of these organisms would agglutinate also with the Parke, Davis & Co. serum at a dilution of 1 to 500 at the end of twenty-four hours, and the latter at a dilution of 1 to 100.

One of the organisms isolated from Lake Roland failed to give positive Widal reactions with three typhoid bloods at a dilution of 1 to 50, while the other gave negative results with the blood from four typhoid fever patients. Of the two other organisms one gave negative Widal's with 5, another with 2 positive bloods when diluted at 1 to 50.

In seven out of forty-two cases of typhoid fever in which typhoid bacilli were isolated by us from the blood the organisms did not agglutinate with immune serum or known typhoid blood. They did, however, agglutinate with the patient's own blood, and the variability in agglutination of the typhoid bacillus is a well established fact. Müller and Graf<sup>6</sup> have shown that the blood from typhoid fever patients shows great differences in the maximum dilution of agglutination when mixed with different strains of typhoid bacilli. In sixty-three cases the maximum dilution was usually about double for one organism than for another type. In nineteen cases the maximum dilution varied from 1 to 50 to 1 to 100 for one organism whilst the other organism failed to agglutinate even with undiluted serum.

Ainley Walker<sup>7</sup> has shown that the strength of agglutination for an antityphoid serum prepared by injecting a horse with dead typhoid bacilli is very much more marked for the bacillus used for the injection than for various other varieties of typhoid bacilli. The serum, therefore, has a special action on its own organism. As an example he mentions a serum which agglutinated its own organism at a dilution of 1 to 300,000 while it agglutinated five other organisms at a dilution of 1 to 100,000, 1 to 90,000, 1 to 80,000, 1 to 75,000, and 1 to 70,000. Later it agglutinated its own organism at a dilution of 1 to 3,000,000 and agglutinated the other organisms only at 1 to 700,000, 1 to 600,000, 1 to 550,000, 1 to 450,000, and 1 to 400,000. All of these typhoid organisms were obtained from cases of typhoid fever.

We have also performed experiments with seven strains of typhoid bacilli isolated from the blood of typhoid fever patients, using one immune serum that agglutinated our laboratory typhoid at 1 to 25,000, and another serum agglutinating this organism at a dilution of 1 to 1,000. The first serum agglutinated two strains at a dilution of 1 to 10,000, two at a dilution of 1 to 5,000, and failed to agglutinate the other two strains even at a dilution of 1 to 50. The second and less potent immune serum agglutinated one strain at a dilution of 1 to 1,000, another at a dilution of 1 to 500, three at a dilution of 1 to 250, while the other failed to agglutinate even at a dilution of 1 to 50.

6. Müller and Graf: *Centralbl. f. Bakteriol.*, 1907, xliii, 856.

7. Walker: *Jour. Path. and Bacteriol.*, 1901, vii, 250.

In comparing our four water organisms and two oyster organisms (to be described later) to five strains of typhoid bacilli isolated from patients, we found that all six of the former organisms would agglutinate at a maximum dilution of 1 to 100 with known typhoid blood, while only two of the case typhoids agglutinated at this dilution. The other three organisms agglutinated at a maximum dilution of 1 to 50. In another instance five case typhoids agglutinated at a dilution of 1 to 250, two agglutinated at a maximum dilution of 1 to 50, and one failed to agglutinate even at a dilution of 1 to 25 with known typhoid blood; one of the water organisms agglutinated at a dilution of 1 to 100 with this blood, and all the other water and oyster organisms failed to agglutinate even at a dilution of 1 to 25.

We have also isolated from market oysters two organisms which correspond to the typhoid bacillus in morphology, motility, staining characteristics, and all cultural properties. These organisms were pathogenic for guinea-pigs, producing purulent peritonitis and general bacteriemia when one-fifth of the washings in salt solution of a twenty-four-hour growth on slanted blood serum 2 inches in length was injected.

One organism gave a positive reaction at a dilution of 1 to 50 with typhoid blood in four cases, and in five cases the reaction was negative. The other organism gave three positive reactions at the same dilution, and five negative results. Neither of these organisms gave a positive result with the Parke, Davis & Co. immune serum at a dilution of 1 to 1,000, although it would agglutinate our laboratory typhoid at this time at a dilution of 1 to 25,000. These organisms did agglutinate with the immune serum prepared from the typhoid organism isolated from the well in about the same dilution at which this serum agglutinated the laboratory typhoid bacillus.

Both of these organisms also agglutinated at a maximum dilution of 1 to 100 with the Kinyoun serum which agglutinated case typhoid bacilli at a dilution of 1 to 1,000.

In attempting to control the typhoid fever in a large city we believe that two distinct lines of investigation should be carried out. In the first place, a careful study should be made of the seasonal distribution of typhoid fever, and if this increase corresponds to the fly season and the city is not properly sewered, a vigorous campaign should be started for a sewerage system. Active measures should be taken to destroy the breeding-places of flies and to prevent their entrance into houses. In the second place, a careful investigation of the water-supply should be made in order to detect the presence of the typhoid bacillus. We believe that this can be best carried out by means of Hesse's medium or our modified

medium. If painstaking investigations carried through many years fail to disclose the typhoid bacillus in the water-supply of a city, it is reasonable to direct the most active measures against the destruction of the typhoid fly. As long as water contains even the colon bacillus, however, it should be boiled or filtered by slow sand filtration.

#### WATER-BORNE TYPHOID IN RURAL DISTRICTS

By means of our modified medium we have been able to detect the typhoid bacillus in a well which was the cause of an outbreak of typhoid fever.

This outbreak occurred in a boarding-school in which there were also day scholars. We were unable to obtain any exact data concerning this outbreak, but were simply informed that it was entirely confined to the boarders, and that none of the day scholars developed typhoid fever. On further inquiry we learned that the boarders drank water from a tank supplied by a certain well. None of the day pupils drank this water. We obtained a sample of the water from the tank and centrifugalized 50 c.c. We inoculated the sediment into lactose bile medium and obtained perfectly typical colonies of the typhoid bacillus on the modified Hesse's medium. This organism was typical in all respects on culture material, and agglutinated by an immune serum at a dilution of 1 to 500. This same immune serum would only agglutinate our stock typhoid at a dilution of 1 to 1,000. The organism also agglutinated with a number of positive typhoid bloods, and on immunizing a rabbit with the organism the rabbit serum agglutinated typical strains of the typhoid bacillus at a dilution of 1 to 1,000. As a final test we found that the serum was opsonic for the typhoid bacillus at a dilution of 1 to 25, and the organism also produced fatal peritonitis in guinea-pigs in doses corresponding to the washings from a two-inch blood-serum slant.

#### ISOLATION OF TYPHOID FROM SEWAGE

We have also obtained the typhoid bacillus from a stream containing much sewage which runs through the center of Baltimore. We have obtained the history of several cases of typhoid fever, which apparently originated from boys bathing in this stream.

This bacillus was typical in all respects, and it agglutinated at a dilution of 1 to 250 with the same immune serum that agglutinated our other water organism at a dilution of 1 to 500. The organism also agglutinated with positive typhoid blood and with the blood serum from the animal immunized with the other typhoid organisms recovered from water.

## MILK-BORNE TYPHOID FEVER

In trying to prevent the occurrence of outbreaks of typhoid fever through milk in our city, an ordinance is enforced which requires physicians to report all cases of typhoid fever to the Department of Health. The health-warden then visits the house and obtains the information included on the accompanying card.

## HEALTH-WARDEN'S REPORT CARD

.....St. No. ....

## TYPHOID FEVER

Health-Warden.....Ward, Reports as Follows:

No. of Cases.....Age.....  
 Male.....Female.....  
 White.....Colored.....  
 Has patient been out of the city during the 3 weeks previous to calling in physician?.....  
 Blood-specimen examined.....  
 Widal reaction.....  
 Milk-supply.....  
 Is the patient a milk-drinker?.....  
 Is milk taken away from home?.....  
 Water-supply.....  
 Name of patient.....  
 .....Health-Warden.

When there are more cases than one in the same family, or in the same house, a card must be filled out for each case.

The city chemist has control of the milk-supply and each case of typhoid fever is credited to the milk-dealer who receives the milk from the shipper on the milk-route. The names of the milk-receivers are arranged alphabetically on cards, and when an unusual number of typhoid fever cases appears on a given route, an inspector is sent to examine the city premises of the milk-dealer for the presence of typhoid fever, or convalescents who may have been handling the milk. If such are found the license is revoked until the offending persons are removed and a further inspection shows that the milk can be sold again with safety.

If no such cases are found, a careful inquiry is instituted concerning a previous attack of typhoid fever, and if a history of the disease is obtained, the stools and urine are examined for typhoid bacilli. This can be easily done now by means of inoculating tubes of lactose bile and plating them out on the special medium which we have described above. A paper by Stokes and Stoner<sup>8</sup> describes a legal mailing outfit in which

8. Stokes and Stoner: Jour. Infect. Dis., 1910, vii, 457.

specimens of inoculated bile can be sent through the mail, and we have found this very useful in detecting carrier cases or dangerous convalescents.

In order not to lose any time, another inspector is sent to the sources of supply of milk used by the shipper, and the same investigations concerning typhoid fever cases, convalescents or carrier cases are made. In either case, if no definite information is obtained the stools and urines of every one handling the milk are examined to see if any carrier cases have escaped observation.

There is one question to be decided before instituting such proceedings, and that is just what constitutes an abnormal number of typhoid cases on a given milk-route. In order to establish what might be regarded as a normal factor we have collected figures giving the approximate number of customers served by 173 of our dairies. We have also obtained the average number of typhoid fever cases on these various milk-routes for six months of the year, and the percentage of these cases when compared with the total number of customers (48,200) is as follows:

January .....	15 cases or 0.03 per cent.
August .....	50 cases or 0.1 per cent.
September .....	57 cases or 0.1 per cent.
October .....	35 cases or 0.07 per cent.
November .....	10 cases or 0.02 per cent.
December .....	16 cases or 0.03 per cent.

It will be seen from the above figures that the normal number of typhoid cases on an uninfected milk-route during any month is not over 0.1 per cent., and the average for these six months is 0.06 per cent. In a typical milk outbreak of typhoid fever the attack rate often rises much above this figure or the monthly figure in which it occurs within the period included by a few days. When the number of cases suddenly appearing within a few days on a given milk-route is seen to exceed the average for the month in which it occurs an inspection of the various sources of supply and delivery along the milk-route should be instituted. As typical examples of milk-borne outbreaks of typhoid fever strangled in their infancy by means of this method we would cite the following instances:

During August, 1909, five cases of typhoid fever were noted within eight days on the milk-route of a city distributor having 325 customers. His typhoid rate was therefore, 1.5 per cent., while the normal rate for August is 0.1 per cent. An immediate investigation revealed that a typhoid fever patient at the dairy farm was being nursed by a milk-handler. The patient was at once removed, boiled water was used for

washington the utensils and after this time only one case occurred, which could by any possibility be attributed to this milk.

In a second instance four cases occurred in September on the route of a dairyman serving 400 customers, showing an attack-rate of 1 per cent., as compared to the normal typhoid rate of 0.1 per cent., for September. An investigation showed a convalescent handling milk in the city dairy. He was prohibited from further work until a later examina-



Fig. 3.—The map for 1906 shows a typical milk epidemic, as shown by the large number of black pins in the upper portion of the map. The rest of the city, when compared with the map of 1907, shows a much smaller number of cases.

tion showed that his stools and urine were free from typhoid bacilli, and no further cases developed from this source.

As another typical example of how quickly a milk outbreak can be checked when the number of typhoid cases rises above the normal factor we would cite this additional instance.

On Sept. 22, 1909, six cases of typhoid fever were reported on the route of a certain milkman who supplied 240 customers. The attack-rate was 2.5 per cent for one day as compared to the normal monthly rate for September of 0.1 per cent. On inquiry it was found that the man who handled the milk on the farm was also nursing a typhoid fever patient, who was then convalescent. This convalescent was removed to a hospital, and the man was required to boil the water used for washing the milk utensils. Seven cases occurred within a period of one week after this, and on October 10 the quarantine was removed and no cases have developed since.

We made an examination of this milk for the presence of the typhoid bacillus but with negative results. This was to be expected, as the man was convalescent and was no longer being nursed by the dairyman. We believe, however, that in such cases the milk should be examined for typhoid bacilli by means of the method we have described above. In 1905 the typhoid bacillus was isolated by Konradi<sup>9</sup> from milk that had caused an outbreak of typhoid fever. As soon as the typhoid factor rises above the normal the milk should be examined for typhoid bacilli. Various investigators<sup>10</sup> have shown that the typhoid bacillus will live in milk for about two weeks and in butter for about three weeks.

In summing up this matter, we believe that when the typhoid milk factor on a route becomes higher than the normal average monthly typhoid milk factor, the various sources of supply should be examined for cases of typhoid fever, convalescents and carrier cases, and as a confirmatory test the milk should also be examined by means of the modified Hesse's medium for the presence of the typhoid bacillus.

#### CARRIER CASES

We have found our modified medium and our mailing cases for inoculated bile very useful in detecting carrier cases both in the city and in the country.

As a typical example of a carrier case producing typhoid fever on a farm we would give the following instance:

A colored boy, aged 12, had lived on the place of Mr. N. all his life, but on May 21, 1909, he began waiting on the table and washing the dishes in the home of his employer. On June 5 Mrs. N. was stricken with typhoid fever and a visitor was also similarly affected. This boy also prepared breakfast at his own home for his younger brothers and sisters, and on June 12 his sister was also attacked with typhoid fever.

9. Konradi: *Centralbl. f. Bakteriol.*, 1905, xl, 31.

10. Trask: *Bull. No. 41, Hyg. Lab. U. S. Pub. Health and Mar.-Hosp. Service*, Washington, p. 24.



Previous to May 21 the boy had never waited on the table or handled any raw food.

We obtained a specimen of his feces and urine in a legal mailing outfit sent by his physician, and the examination by means of the modified Hesse's medium revealed the presence of the typhoid bacillus in his stool. The boy gave no history of a typhoid attack, and this case was probably one of those latent infections of the gall-bladder which would have escaped notice without a bacteriologic examination. Other duties have been assigned to this boy and no further cases of typhoid have developed.

#### INSTITUTIONAL TYPHOID

We have studied two very interesting outbreaks of typhoid fever which were produced by carrier cases. The details of these outbreaks were as follows:

The first outbreak occurred in a home for young women who pay a moderate board and earn their own living. The house contained fifty inmates and three servants. The water was boiled and the milk was pasteurized. The raw vegetables were washed at the tap before use. From March to May, 1908, ten cases of typhoid fever occurred among the inmates, and one in a child of one of the domestics who visited the kitchen frequently and ate meals at the "home." From September to December three more cases developed in the institution, making an attack rate of 25.0 per cent. between March and December.

Without giving unnecessary details we would simply add that cultures from the urine and feces were taken from every inmate of the "home," including the servants, and suspicious colonies were studied in a thorough manner. We found typhoid bacilli in one of the stools of a convalescent, but as she did not handle food we disregarded this finding. We also found many typhoid colonies in the stool of one of the domestics, who had entered the home in December, 1907. This domestic cut the bread and handled all the raw foods excepting the milk. She was removed from the kitchen, and no further cases have occurred up to the present time.

The second outbreak occurred in a convent and home for colored children. This institution contained thirty-seven sisters, forty-seven colored girls, and ten deaf-mutes. Three domestics also worked in the kitchen, and an engineer and two assistants are employed at the institution. The water was boiled and cooled in bottles. The milk was obtained from a dairy, the route of which showed no increase of the typhoid-rate. Although it was not pasteurized, yet in view of this fact and considering that a number of the patients were not milk-drinkers, and that the attack rate among the users of the milk was only 2.0 per cent., we felt justified

in eliminating this as the source of the infection. It was recommended, however, that the milk be pasteurized. The method of disposal of sewage in the institution was good, and as there was no cesspit in the yard, and the general surroundings were in good sanitary condition, we considered the typhoid fly as a negligible quantity as a means of transmission. As the laundry was thoroughly disinfected, and as none of the inmates or sisters handling it developed the disease, this was disregarded as a means of infection.

In studying this outbreak we found that eight cases had developed, and these were readily separable into two groups of four each. The first group included four of the sisters who had frank cases of typhoid, and had used in the toilet towels in common with one of the sisters who later proved to be a carrier. The other group included four of the colored children and deaf-mutes. These, as their blood failed to agglutinate the typhoid bacillus but readily clumped several strains of *B. paratyphosus*, were considered cases of paratyphoid fever. In addition to this we isolated the *B. paratyphosus* from the stools of all four children.

We obtained specimens of stools and urine of all persons in any way connected with the handling and serving of food, and also from two other inmates who had had typhoid fever within the past two years. These, after preliminary cultivation in lactose bile, were plated out on modified Hesse's medium and suspicious colonies picked and studied in a thorough manner. As a result of this study we found that two of the sisters were typhoid and three were paratyphoid carriers. Of the former, one was in the kitchen while the others were closely associated with the sisters who developed typhoid fever, as before mentioned. Of the latter, one was also associated with the handling of food and the others were in intimate contact with the paratyphoid cases. After removal of these from the kitchen, and after special towels had been provided for all carriers, no more cases developed.

In this paper we have not tried to describe all of the methods which are useful in preventing the spread of typhoid fever, but have simply mentioned certain kinds of outbreaks which may be studied mainly by laboratory methods.

In conclusion we desire to thank Dr. C. Hampson Jones, Assistant Commissioner of Health, for the photographs, and Dr. H. W. Stoner for the photographic reproductions.

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## A STUDY OF THE TYPE OF INFANTILISM IN HOOKWORM DISEASE\*

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A search of the literature has shown that no one has yet given more than cursory notice to the striking infantilism of hookworm disease. So striking is the phenomenon that authorities have contented themselves with mentioning its existence as a well-known fact. The subject is dismissed with the general statement that hookworm victims are undersized, lack pubic and axillary hair and show other evidences of lack of development.

It is the purpose of this paper to report in detail the exact study of the grade of development in a case of hookworm disease and, by contrasting it with other types of infantilism, to endeavor to fix its classification.

*Personal History.*—O. J., a white male, aged 22, from Biloxi, Mississippi, was admitted to the Charity Hospital, April, 1909, for treatment for anemia secondary to hookworm infection. He had ground-itch for the first time when he was 6 years old and had it every summer until he stopped going barefoot at the age of 19. He has not grown since he was 12 years old. From his tenth year he used to "bloat up" and did not feel like going about. This lasted for five or six years, but from his sixteenth year he has been pretty well except that he tired easily. He attended school off and on from the time he was 5 years old—altogether for perhaps three years. When he left school at 14 he was in the seventh grade. He had no difficulty with his lessons and always stood near the top of a class of from ten to twenty-five. At 17 he was sick a whole summer with fever, which was diagnosed as malaria. He had measles at 14 and mumps at 21. The diagnosis of uncinariasis was made by a physician who was called to see him because of a slight cold. He was first treated at the Touro Infirmary in November, 1907, and felt a great deal better after his treatment there. He returns now for treatment because he fatigues easily. He has lived at various times in the following places (all in Mississippi): Biloxi, Pass Christian, Orrisburg, Poplarville, Hattiesburg.

*Family History.*—The father died of typhoid, but the mother is living and well. One brother is living and well, 20 years old, weighs 160 pounds; he has had ground-itch a few times. Two sisters, 17 and 20 years old, respectively, are living and well. Each weighs 115 pounds. Neither has had ground-itch. The patient says that his brothers and sisters are well developed.

*Present Condition.*—The patient is a small, pale, sallow individual, apparently about 13 or 14 years old. His intelligence is good. His answers are quick, his skin is dry, his hair is thick and coarse and there are areas of alopecia over the occiput.

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\*From the Clinic of Prof. George Dock, Tulane University of Louisiana.

Thorax: Heart not enlarged; no murmurs. Lungs normal.

Abdomen: No distention. Liver is not enlarged.

Spleen is not palpable. Slight tenderness on pressure over the epigastrium.

Wing scapulae.

No axillary or pubic hair.

Genitalia correspond in size and development to apparent age of patient.

The following blood-picture (made May 10, 1909) is representative of a number of blood examinations made from time to time:

Hemoglobin, 45 per cent.; red blood cells, 4,160,000 to the c.mm.; leucocytes, 7,600 to the c.mm. Eosinophils, 9% per cent.

Examination of stools showed ova of *uncinaria* still present.

Measurements:

Skull:

Fronto-occipital circumference, 53.5 cm.

Mento-vertical circumference, 57 cm.

Mento-occipital circumference, 61 cm.

Chest:

Full inspiration (at nipple level), 70.25 cm.

Full expiration (at nipple level), 63.75 cm.

Full inspiration (at level of armpits), 63.5 cm.

Full expiration (at level of armpits), 58.5 cm.

Full inspiration (at base of chest), 64.75 cm.

Full expiration (at 8th rib), 58 cm.

Height standing, 139.5 cm.

Distance from umbilicus to the ground, 85 cm.

Distance from the tip of his fingers (placed on his thigh while standing) to the ground, 54.5 cm.

Upper extremity:

Acromion to olecranon, left, 27.5 cm.; right, 27 cm.

Olecranon to tip of middle finger, left, 37 cm.; right, 37.25 cm.

Ulna, left, 22 cm.; right, 22 cm.

Hands:

Thumb (right) metacarpal, 5 cm.; first phalanx, 2 cm.; second phalanx, 2.5 cm.; (left) metacarpal, 5 cm.; first phalanx, 2.5 cm.; second phalanx, 2 cm.

First finger (right) metacarpal, 7 cm.; first phalanx, 3.25 cm.; second phalanx, 2.5 cm.; third phalanx, 1.5 cm.; (left) metacarpal, 7 cm.; first phalanx, 3.5 cm.; second phalanx, 2.5 cm.; third phalanx, 1.5 cm.

Second finger (right) metacarpal, 7 cm.; first phalanx, 4 cm.; second phalanx, 3 cm.; third phalanx, 1.5 cm.; (left) metacarpal, 7 cm.; first phalanx, 3.5 cm.; second phalanx, 2.5 cm.; third phalanx, 2 cm.

Third finger (right) metacarpal, 7 cm.; first phalanx, 4 cm.; second phalanx, 2.5 cm.; third phalanx, 1.5 cm.; (left) metacarpal, 7 cm.; first phalanx, 4 cm.; second phalanx, 2 cm.; third phalanx, 1.5 cm.

Fourth finger (right) metacarpal, 6 cm.; first phalanx, 3 cm.; second phalanx, 1.5 cm.; third phalanx, 1.5 cm.; (left) metacarpal, 6 cm.; first phalanx, 2.5 cm.; second phalanx, 1.75 cm.; third phalanx, 1.5 cm.

Pelvis:

Circumference over crest of ilia, 56 cm.

Circumference over great trochanters, 58 cm.



Fig. 1.—Patient affected with hookworm infantilism, front view.



Fig. 2.—Same patient as in Figure 1, side view.

## Lower extremities:

From anterior superior spine of ilium to internal condyle, both sides,  
43.5 cm.

From anterior superior spine of ilium to external malleolus, both sides,  
75.5 cm.

Length of feet, 20.5 cm.

It will be noticed that the dwarfing process is uniform. There is no disproportion between the lengths of the limbs and that of the trunk, and no undue size of the extremities or of the head.

Skiagraphs of the long bones of the thorax and of the pelvis show no deformity and no abnormality of any kind. There is no bowing of the shafts of the long bones, no thickening of their ends, no evidence of abnormal cartilage processes in the epiphyses, no thickening of the periosteum. The ribs are apparently of uniform thickness throughout. The pelvis is symmetrical and of proper size in proportion to the rest of the skeleton.

As a standard by which we may estimate the degree in which our patient's growth has been retarded, I have adopted the suggestion of Rotch<sup>1</sup> and have attempted to arrive at the anatomic age of the patient by comparing his skeleton with those of the average normal individual. For this purpose Rotch has used the skiagraphs of the bones of the wrist and has by a series of observations of normal wrists fixed a standard of development for each age. The skiagraph of my patient's wrist shows seven carpal bones well developed, namely, the scaphoid, semilunar, cuneiform, trapezium, trapezoid, os magnum, and unciform. In addition, the lower epiphyses of both ulna and radius are well developed. The shadow of the pisiform bone is barely to be seen. A reference to Rotch's table would place this wrist in Class K and cause us to estimate the true anatomic age of our patient as about 10 or 11 years. This is the estimate placed by Dr. Rotch, to whom the skiagraph has been submitted. We may conclude, therefore, that hookworm infection may retard the developmental changes to such an extent as to cause an individual of 22 to retain the grade of ossification of the average normal individual of 10 or 11.

The infantilism of hookworm disease has much in common with infantilism from certain other causes. On the other hand there are some forms of arrested development with which it stands in strong contrast and with which it is not likely to be confused. Such types are, for example, the achondroplastic dwarf, the mongolian idiot, the rachitic dwarf. From the achondroplastic dwarf, my patient is readily distinguished by the absence of the characteristic lack of proportion between the lengths of the extremities and that of the trunk. Besides there is no trident hand, no bowing of the long bones, no decentralization of the umbilicus, no prognathism as there usually is in achondroplasia. The genitalia share in the retardation, while in achondroplasia they correspond in size

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1. Rotch, T. M.: Chronologic and Anatomic Age in Early Life, *Jour. Am. M. Assn.*, 1908, li, 1197.

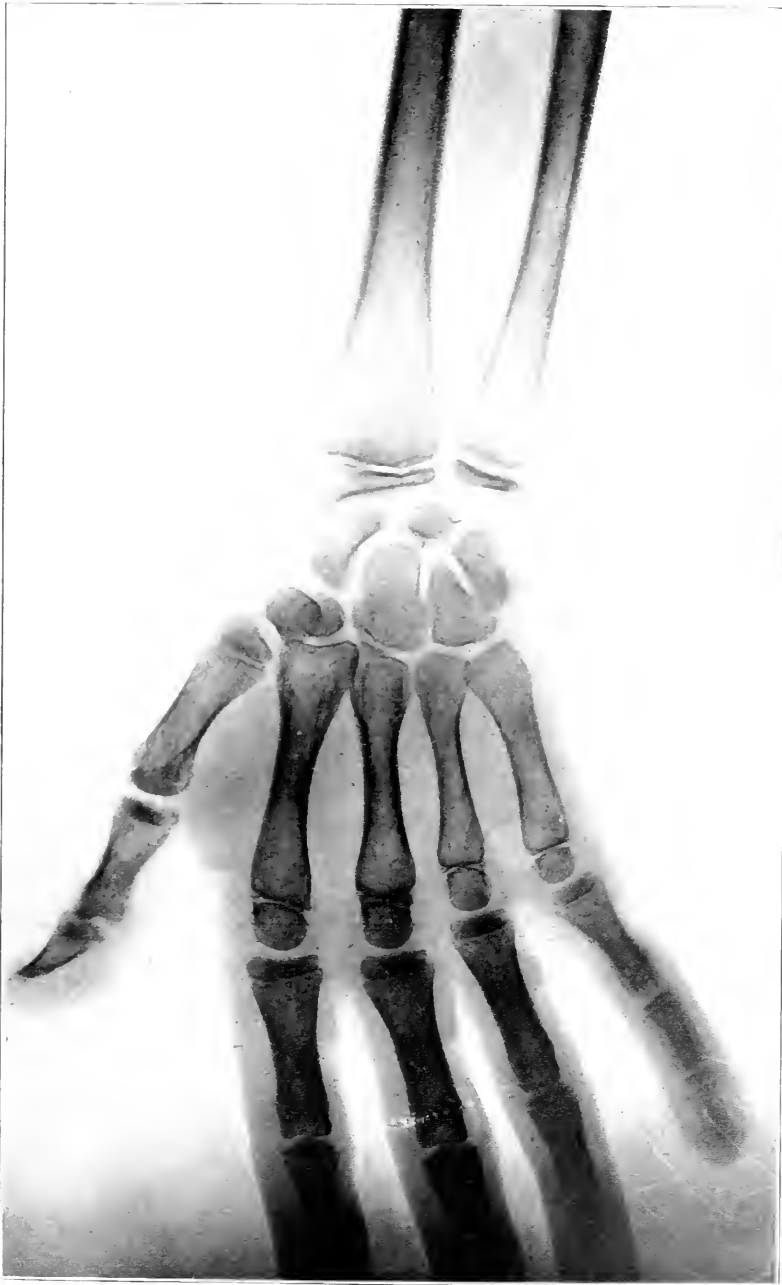


Fig. 3.—Skiagraphic view of patient's hand.

and development to the true age of the individual. The skiagraphs of the hookworm dwarf show none of the cartilage changes of the achondroplastic. The hookworm dwarf has equally as little in common with the rachitic dwarf. In rickets the bone shadow is paler than normal and the medullary canal is larger, making the cancellous tissue smaller. Hence there is a bending and bowing of the long bones. The ends of the long bones are enlarged and there is irregular cartilaginous development of the epiphyses. In addition there is an unduly large skull, squared and frequently "bossed." None of these features are present in the hookworm dwarf.

There could be no question of the difference between the hookworm infantile and the outspoken fully developed cretin. The latter, with his thick, protruding lips, big head, short thick neck, long cylindrical torso, lumbar lordosis and infantile pelvis, his thick skin and marked adiposity, as well as his drooling idiocy, presents a picture not to be confused. If the hookworm dwarf has no mental characteristics in common with the cretin, he has equally none with the mongolian idiot. In addition, he lacks the slant-eyed mongolian facies.

But there is a masked cretin, the dysthyroid or hypothyroid infantile (type Brissaud) who may have a much closer resemblance to our patient. In both there is a simple retardation of the development in general, involving not only the skeleton but the genitals and the secondary sexual characteristics; in both there may be a dry skin with dry, harsh, scanty hair. But even the masked cretin, fairly intelligent though he may be, has usually enough of the characteristics of the cretin, namely, the round full face with thick lips, small nose and thick skin, to distinguish him from the patient of the type of ours. It may not be out of place here to repeat the suggestion often made before, that infantilism of widely differing fundamental causation may be due to disturbance of the function of the thyroid and other ductless glands with internal secretion. In this sense, therefore, hookworm infantilism may be a dysthyroid condition. After all, infantilism is only a symptom-complex, not a disease. What the actual pathologic lesion is, is still to be determined for hookworm infection as for many other causative factors; it may be thyroid, pituitary, ovarian, testicular, etc., etc. The only point I wish to make here is that the masked cretin and the hookworm infantile do not differ markedly in kind, a fact suggesting a possible relation of pathology.

The cases reported by Ettore Levi<sup>2</sup> show that the infantilism of the type Lorain presents skeletal changes not different in kind from those in my case. The type Lorain infantile has been described as having a small

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2. Levi, Ettore: *Nouv. iconog. de la Salpêtrière*, 1908, xxi, 421.





Fig. 4.—Skiagraphic view of normal adult hand for comparison.

stature, delicate, slender skeleton and form, long, slim legs, relatively small trunk, infantile sternum and pelvis, long neck with fine, pale skin, and no adipose envelop. The genitals are small and the secondary sexual characteristics are usually lacking. The dimensions of the body in general are small and the proper relation between the various parts is well preserved. An excellent example of the type is the case reported by Dr. Van Wart and myself<sup>3</sup> in the May number of *THE ARCHIVES OF INTERNAL MEDICINE*. We considered the cause of this case to be pituitary tumor, which was also a probable cause in one of Levi's cases. But infantilism of this type is also not to be considered a distinct entity from the standpoint of etiology. On the whole our hookworm infantile conforms neither to the type Brissaud (dysthyroid or athyroid) nor to the type Lorain in his general appearance, suggesting rather the second than the first and standing midway between the two. The retarded development said to be due to chronic malaria is probably analogous to that of hookworm infection and Levi speaks of Lancereaux and Ferrarini's malarial cases as being of the Lorain type. Pellagra (hereditary) has also been held responsible for a similar form of infantilism.

I have found no skiagraphic study of infantilism of the type Lorain due to such causes as hereditary syphilis (unless Levi's are to be so regarded), tuberculosis (of the parents), mitral stenosis, alcohol, lead, nicotin, etc., but it seems more than probable that they would show simply a general retardation without special changes in bone or cartilage.

I conclude, therefore, that the infantilism of hookworm disease shows in general the following characteristics:

1. A general retardation of growth, symmetrical and harmonious.
2. A simple retardation of skeletal changes.
3. A failure of development of the genitals as well as the absence of secondary sexual characteristics.
4. A mental slowness and dulness (not present in my patient).
5. A general appearance which conforms neither to the Brissaud nor the Lorain type.

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3. Lemann, I. L., and Van Wart, R. M.: A Case of Infantilism with Absence of Thyroid and Tumor of Pituitary, *THE ARCHIVES INT. MED.*, 1910, v, 519.

## TROPHONEUROTIC CHANGES IN BONES AND JOINTS IN LEPROSY \*

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It is well recognized that in leprosy, especially its anesthetic form, marked deformities of the hands and feet may develop. Such cases are generally designated as "lepra mutilans." Many, perhaps the majority of these cases, are dependent on ulceration, necrosis, and chronic suppurative inflammation, which in turn are indirectly due to a chronic leprous neuritis with its accompanying anesthesia and analgesia. Necroses or ulcers form, phalanges gradually slough off, and finally the characteristic, clubbed hands and feet of leprosy are formed. The accompanying illustrations of such hands and feet show their appearance in some very pronounced cases. This explanation does not hold in all cases, however, as some of these deformities are to be ascribed to a peculiar trophoneurotic influence which is probably directly exerted by the neuritis on the tissues, especially those of the osseous system, and which may result in atrophy of bone of characteristic appearance, and in certain joint affections.

The first to call attention to the occurrence of such atrophies of bone in leprosy was the late Prof. H. Heiberg,<sup>1</sup> whose work on this subject, published in 1886, has received little attention, although it contains interesting observations and touches on questions of importance in physiology and general pathology. Since then, little has been written on this subject (Deycke, Hirschberg and Bichler). I therefore have desired to renew the study of this problem<sup>2</sup> and questions arising with it, and will present the results in the following pages. I feel especially inclined to do this, having had at my disposal most excellent, and in some respects, unique material, partly from our pathologic institute in Christiania, and partly from the leprosy hospital in Bergen, which latter material was

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\* An abstract of this paper, illustrated by specimens, photographs and diapositives, was read before the Second International Leprosy Conference, held at Bergen, Norway, Aug. 16-19, 1909.

1. Heiberg, H.: *Om lepra mutilans og trofoneurotiske forandringer ved spedalskhed*, Klin. Aarborg., 1886, iii.

2. I have discussed this subject once before, in my competitive thesis for the professorship in pathologic anatomy and general pathology, entitled *Om de pathologisk-anatomiske forandringer af neurotrofisk oprindelse*, Christiania, 1900, A. W. Brögger's Buchdruckerei. This work is especially devoted to microscopic investigations of these atrophies.

kindly placed at my disposal by Dr. H. P. Lie. As will be seen by the case reports, the material was obtained from patients who had suffered from leprosy from fifteen to sixty-seven years, during most of which time they had been under observation in our leprosy hospitals.

#### SPECIMENS

**SPECIMEN 1.**—Concentric atrophy of finger phalanges (Fig. 1). The skeleton of the right hand of a leprosy patient. The carpus is on the whole normal. The metacarpal bones also have their usual appearance, but are somewhat thin, rather short, especially in the diaphyses, but have capitula of usual appearance. They measure in length (from No. 1 to 5, respectively) 4.5 cm., 6.4 cm., 6 cm., 5.8 cm., and 5.2 cm. Of the phalanges, only the first one is preserved and merely



Fig. 1.—Right hand: concentric atrophy of the phalanges.

the shape of pieces of bone markedly pointed anteriorly, and measuring 3.8 cm. (phalanges grown together), 1.4 cm., 2.5 cm., 2.2 cm. and 2 cm. Hence the second and third phalanges are missing in the last four fingers.

**SPECIMEN 2.**—Atrophy of the finger phalanges (Fig. 2). Left hand of a patient with anesthetic leprosy who contracted the disease in 1820, was admitted to the Reknäs Hospital for lepers in 1875, and died of peritonitis in 1887, sixty-seven years after the onset of leprosy. The feet were greatly deformed on account of extensive carious processes. The left hand was club-shaped on account of necrosis of the phalanges. The specimen shows that the carpus is preserved, and the metacarpal bones are about normal. The fingers are flexed at right angles at the metacarpophalangeal joints, pointed anteriorly, and defective. The measurements are as follows:

Os metacarpi I, 5 cm.: Phalanx I, 3.6 cm.: Phalanx II, 2 cm. (normal).

Os metacarpi II, 7.2 cm.: only one phalanx, 3 cm. long, markedly pointed anteriorly.

Os metacarpi III, 6.8 cm.: only one rudiment of a phalanx.

Os metacarpi IV, 6 cm.: only one phalanx (No. 1 ?), 4.6 cm. long, of usual appearance.

Os metacarpi V, 5.2 cm.: only one phalanx (No. 1 ?), 3.5 cm. long, of usual form with a small rudiment anteriorly 1.4 cm. long.

SPECIMEN 3.—Concentric atrophy of the phalanges of the fingers (Fig. 3). Right hand from a patient with lepra anesthetica (patient whose foot is described as Specimen 8). The hand is deformed, shortened, extended at the wrist, and



Fig. 2.—Left hand: atrophy of phalanges.

the fingers are greatly shortened. The otherwise normal carpus, here and there, presents knobby projections (in part due to chronic arthritis deformans?). The metacarpal bones are nearly normal, but the phalanges are few in number, small, pointed anteriorly, and partly placed at right angles to the metacarpal bones. The measurements are as follows:

Os metacarpi I, 4.5 cm. long: both phalanges missing.

Os metacarpi II, 6.1 cm. long; only one phalanx, 1.8 cm. long, pointed anteriorly.

Os metacarpi III, 5 cm. long; one phalanx (No. 1 ?), 1.8 cm. long.

Os metacarpi IV, 5.6 cm. long; one phalanx 2.1 cm. long, pointed anteriorly.

Os metacarpi V, 5 cm. long; one phalanx 2 cm. long.

**SPECIMEN 4.**—Some degree of atrophy of the finger phalanges (Fig. 4). The specimen is the left hand (the right foot is Specimen 5) of a patient with lepra anesthetica with onset in 1861, admittance to a leprosy hospital in 1864, and death in 1887, or twenty-six years after the onset. Already in 1864, there was considerable paresis of the face, the upper and particularly the lower extremities, with loss of sensation. The left hand, removed at necropsy, shows the following conditions: The carpus is entirely normal. The metacarpal and phalangeal bones also are of about usual size and shape. The position, with the fingers markedly flexed, is that known as "claw-hand."



Fig. 3.—Right hand; concentric atrophy of phalanges.

Os metacarpi I, 4.6 cm.; Phalanx I, 3 cm.; Phalanx II, 2 cm.

Os metacarpi II, 6.3 cm.; Phalanx I, 2 cm., pointed; Phalanx II, 1.5 cm., thin in the middle; Phalanx III, 1.4 cm., pointed.

Os metacarpi III, 6.2 cm.; Phalanx I, 4.7 cm., pointed; Phalanx II, 3.1 cm.; Phalanx III, 1.6 cm.

Os metacarpi IV, 5.3 cm.; Phalanx I, 3.2 cm.; Phalanx II, 2.6 cm.; Phalanx III, 1.7 cm.; all bones nearly normal.

Os metacarpi V, 5 cm.; Phalanx I, 3.5 cm.; Phalanx II, 2.4 cm.; Phalanx III, 1.2 cm.; all bones nearly normal.

**SPECIMEN 5.**—Ulcerative-necrotic inflammation of the tarsus (*lepra mutilans*); typical concentric atrophy of the fourth and fifth metatarsal bones and loss of phalanges of the fifth toe. In the right foot (same patient as Specimen 4), there

had been a carious-necrotic process, so that the foot at necropsy was found to be loosened at the ankle, being attached only by the soft parts. The foot was of about normal length, but unusually narrow on account of atrophy of its outer portion. The tarsus shows great changes. The calcaneum is 7.8 cm. long, tapers forward, and shows necrosis on the inner side and at the anterior end. The talus, os cuboideum, and os naviculare, as well as the cuneiform bones II and III, are nearly entirely wanting, while a considerable part of os cuneiforme I is intact. The greater part of the metatarsal bones is preserved; there is atrophy only on the fibular side.



Figure 4.



Figure 5.

Fig. 4.—Left hand; moderate atrophy of phalanges.

Fig. 5.—Right foot; lepra mutilans; concentric atrophy of fourth and fifth metatarsal bones.

Os metacarpi I, 6.2 cm.; Phalanx I, 3.3; Phalanx II, 2.5 cm.; all nearly normal.

Os metacarpi II, 7 cm.; Phalanx I, 3.2 cm.; Phalanx II, 1.8 cm.; Phalanx III, 1.2 cm.; all nearly normal.

Os metacarpi III, 6.8 cm.; Phalanx I, 2.7; Phalanx II, 1.6 cm.; Phalanx III, 1.4 cm.; all nearly normal.

Os metacarpi IV, 3.2 cm.; small, atrophic, with thin shafts like narrow edges; knobbed anterior ends; Phalanx I, 2.6 cm.; Phalanx II, 1.5 cm.; Phalanx III, 1.2 cm.

Os metacarpi V, 2.5 cm.; small, atrophic, with thin shafts like narrow edges; knobbed anterior ends; Phalanx I, 1.7, atrophic and pointed anteriorly; both the other phalanges missing.



Figure 6.

Fig. 6.—Left foot: concentric peripheral atrophy of metatarsal bones and phalanges.



Figure 7.

Fig. 7.—Right foot: atrophy of metatarsal bones and phalanges.

SPECIMEN 6.—Previously described in brief by H. Heiberg. Typical concentric peripheral atrophy of the metatarsal bones and of the phalanges (Fig. 6). The skeleton of the left foot of a leprous man 38 years old. The foot is small.



measuring 17 cm. in length. There is concentric atrophy of the metatarsal bones and phalanges, especially in their anterior portions. The entire tarsus shows normal conditions with well-developed bones and joints. The tarsal bones on the whole are of normal size, although the calcaneum is possibly somewhat short. The metatarsal bones, on the other hand, are small, atrophic, and greatly



Figure 8.



Figure 9.

Fig. 8.—Left foot: concentric atrophy of metatarsal bones and phalanges.  
 Fig. 9.—Right foot: ulcerative-necrotic inflammation of tarsus; atrophy of several metatarsal bones.

shortened. They measure, respectively, 2.8 cm., 3.7 cm., 3.6 cm., 4.4 cm., 6.3 cm., and compared to the average length of the metatarsal bones in four normal feet, the shortening is, respectively, 3.5 cm., 3.9 cm., 2.6 cm., 1.8 cm. Their shape is also considerably changed. Their width at the base is about normal, but they taper

considerably and unevenly forward and become pointed in a conical manner. The heads of the metatarsal bones are nearly entirely absent, as far as the three middle toes are concerned. The surface of the bones as a rule is smooth. Only rudiments of the phalanges are left, which are atrophic, thin and pointed, tapering forward. In places they are so thin that a thin wire can scarcely be passed through them. The osseous substance is porous. Only small remnants remain of some of the bones. If the atrophying process had continued, the bones certainly would have become entirely resorbed.



Fig. 10.—Left foot; *lepra mutilans*.



Fig. 11.—Left foot; same as Fig. 10, showing fusion of tibia and fibula.

**SPECIMEN 7.**—Typical atrophy of metatarsal bones and phalanges. Right foot with tendons and joints from a leprosy patient. The foot is small and atrophic, partly on account of defective and hyperextended toes, and partly from a considerable atrophy of the metatarsal bones. The tarsus on the whole is normal; the bones are well developed without nodular projections. The various joints show no actual signs of arthritis. The tendons and ligaments are normal. On the other hand, all metatarsal bones are very atrophic in characteristic man-

ner, the anterior ends being pointed with entirely atrophic heads. The atrophy is most marked laterally, so that the individual bones are cone-shaped.

Os metatarsi I is 3.5 cm. long, somewhat thin, anteriorly in bony ankylosis with Phalanx I, which is 2.2 cm. long, and in turn, ankylosed to Phalanx II, which measures 1.8 cm. long. Both are pointed anteriorly.

Os metatarsi II is 4.5 cm. long, pointed, and attached anteriorly by a lax-joint-capsule to a thin atrophic Phalanx I scarcely 2 cm. long.

Os metatarsi III is 4.2 cm. long, pointed, articulates with a thin phalanx 2 cm. long, which has a thin, bony shell attached to its head.

Os metatarsi IV is 4.3 cm. long, pointed, without phalanges.

Os metatarsi V is 5.5 cm. long, and has a single phalanx, which is awl-shaped anteriorly.

SPECIMEN 8.—Considerable concentric atrophy of the metatarsal bones and phalanges (Fig. 8). Left foot of a patient with lepra anesthetica beginning in

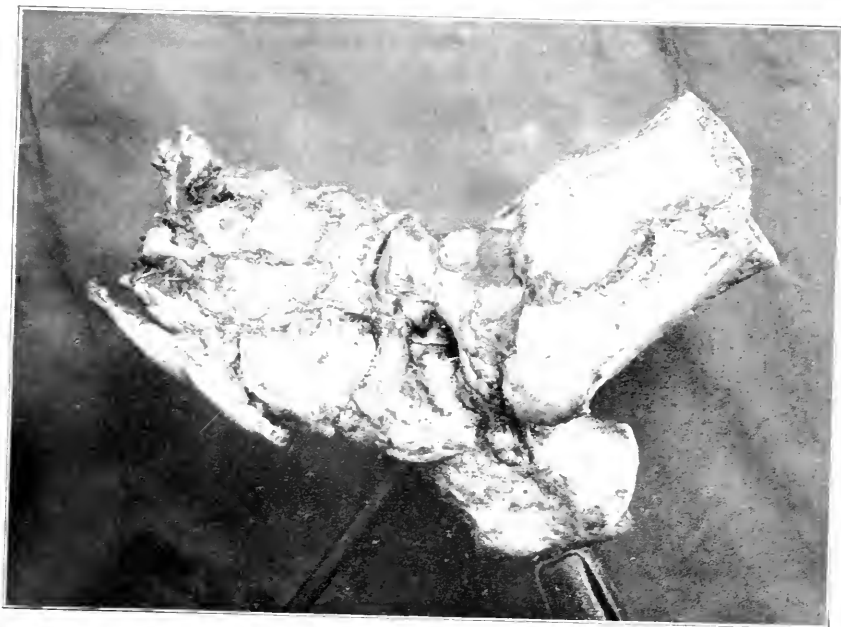


Fig. 12.—Left foot; chronic deforming arthritis of tarsal joints; atrophy of metatarsal bones and phalanges.

1849. On account of ulceration and persistent pain the left foot was amputated in 1888, or thirty-nine years after the onset of the disease. The foot is short and much deformed, chiefly on account of considerable atrophy of the metatarsal bones and, to a lesser extent, of the phalanges. The tarsal bones are normal with the exception of the cuboid, which is short, 1.5 cm. long, and compressed with somewhat rough edges. The metatarsal bones show considerable changes, being in part shortened, narrow and thin, and in part almost entirely resorbed. The same is true of the phalanges, of some of which only rudiments are found. There is no evidence of necrosis or ulceration either in the metatarsal or the phalangeal bones.

Os metatarsi I, 4 cm. long; Phalanx I, 1.7 cm.; Phalanx II, 2 cm. Bones about normal in form and size.

Os metatarsi II, 4 cm. long, thin and pointed; Phalanx I, 2.2 cm.; Phalanx II, 1.2 cm.; Phalanx III, 1 cm. The phalanges about normal; flexed.

Os metatarsi III is 3.5 cm. long, awl-shaped anteriorly with two fragments of phalanges, respectively 1 and 0.8 cm. long.

Ossa metatarsi IV and V have almost disappeared; represented by fibrous cords with small pieces of bones. Phalanges also represented by fragments not over 1 cm. long.

SPECIMEN 9.—Ulcerative necrotic inflammation of the tarsus (Fig. 9). Atrophy of several metatarsal bones. Right foot obtained from a patient with lepra anesthetica with onset about 1877 and amputation of the foot about fifteen years later. The foot is considerably shortened and deformed, chiefly from severe atrophy and destruction of the tarsus, and partly from atrophy of the metatarsal bones and phalanges. Of the tarsus only the posterior part of the calcaneum



Fig. 13.—Right foot; atrophy of tarsus with arthropathies; concentric atrophy of third, fourth and fifth metatarsal bones.

remains. The talus is much deformed. The os naviculare is very defective and irregular in shape. The cuboid is missing and, of the cuneiform bone, only small spicules remain joined into a plate. Probably ulceration and necrosis of the bones had caused these deformities. The metatarsal bones also show great changes, especially the last three, which are shortened, pointed, and partly fused posteriorly. The phalanges, on the other hand, are mostly normal.

Os metatarsi I, 5.5 cm.; Phalanx I, 2.6 cm.; Phalanx II, 1.8 cm.; normal.

Os metatarsi II, shaft shortened, 5.9 cm.; Phalanx I, 2.1 cm.; Phalanx II, 1.1 cm.; Phalanx III, 0.8 cm.

Os metatarsi III, 5 cm.; Phalanx I, 2 cm.; Phalanx II, 1.1 cm.; Phalanx III, 0.9 cm.

Os metatarsi IV, 3.2 cm.; Phalanx I, 2 cm.; Phalanx II, 1 cm.; Phalanx III, 0.8 cm.

The third and fourth metatarsal bones are fused posteriorly, thin, and greatly shortened. On the outside, they are joined by a bony plate 1.5 cm. long, which is probably a rudiment of the fifth metatarsal bone. At the anterior end of this bone is attached the first phalanx, 2 cm. long, with the second phalanx 1 cm. long.

**SPECIMEN 10.**—*Lepra mutilans* of one foot following an ulcerative inflammation. Also concentric atrophy of the metatarsal bones and phalanges (Figs. 10 and 11). The specimen was obtained from a patient with *lepra anesthetica* who contracted the disease in 1852 and died in 1888. There had been ulceration of the sole of the left foot. The big toe had been dis-articulated in 1882. The left foot was secured at the necropsy. It is greatly deformed, forming a lumpy mass, which is in strong, plantar flexion at the ankle. The tibia and fibula are fused for a distance of 5 cm. at the lower end, forming one pointed bone which has united to the remains of the tarsus. The latter consists mainly of the greater part of the calcaneum (7 by 4 by 3.5 cm.) of entirely irregular shape, and pointed anteriorly. To its inner side there adheres a small, smooth, flat piece of bone.

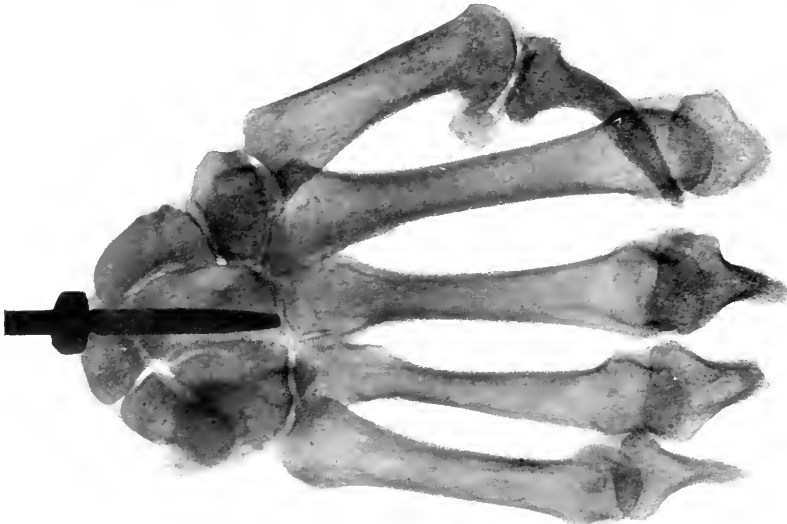


Fig. 14.—Skiagraph; same as Fig. 1.

evidently remains of the talus, and a splinter of bone adheres on the outside (remains of cuboid?). In addition, there remains of the tarsus only a flattened finger-bone, 3.5 by 2.5 cm., the origin of which can no longer be recognized. These marked changes in the tarsus are probably connected with the ulcerative and inflammatory process in the *planta pedis*. Of the metatarsus also, only fragments remain, partly in bony connection with the tarsus. The first metatarsal bone is missing, having probably been removed with the hallux. The second metatarsal bone is 2 cm. long and evenly reduced in all dimensions with a relatively large head. The third metatarsal bone is much smaller and thinner, and of the fourth one, only minute pieces are found. The fifth is unrecognizable. The toes are spread out in a fan-shaped manner from the small atrophic tarsus. The hallux is missing. In the second toe the first phalanx measures 2.4 cm. in length and is very thin at its middle; the second phalanx 0.7 cm. long and the third phalanx 0.7 cm. long, are about normal in size and shape. In the third toe, the first phalanx is 3 cm. long, thin and evenly atrophic; the second phalanx 0.9 cm. long, and the third phalanx 1.2 cm. long, are of about normal size and shape.

The first phalanx of the fourth toe is 1.5 cm. long and evenly reduced in all dimensions; the second phalanx is 1.2 cm. long; the third phalanx is missing. The first phalanx of the fifth toe is replaced by a fibrous cord and continues with the second phalanx which is 0.9 cm. long; the third phalanx is missing.

**SPECIMEN 11.**—Chronic deforming arthritis of the tarsal joints. Typical atrophy of the metatarsal bones and phalanges (Fig. 12). The specimen, obtained from Leprosy Hospital No. 1 in Bergen, is the left foot of a patient with lepra anaesthetica which commenced in 1862. He died of pneumonia in 1889. There were three ulcers on the left foot and necrosis of the fourth toe. The left foot, which was secured at the necropsy, is greatly deformed and markedly shortened on account of shortening or complete absence of metatarsal bones and phalanges. All of the tarsal bones are intact and of about the usual size and shape. The calcaneum being 7 cm. long, the talus 5 cm. and the cuboid 3.2 cm. They are

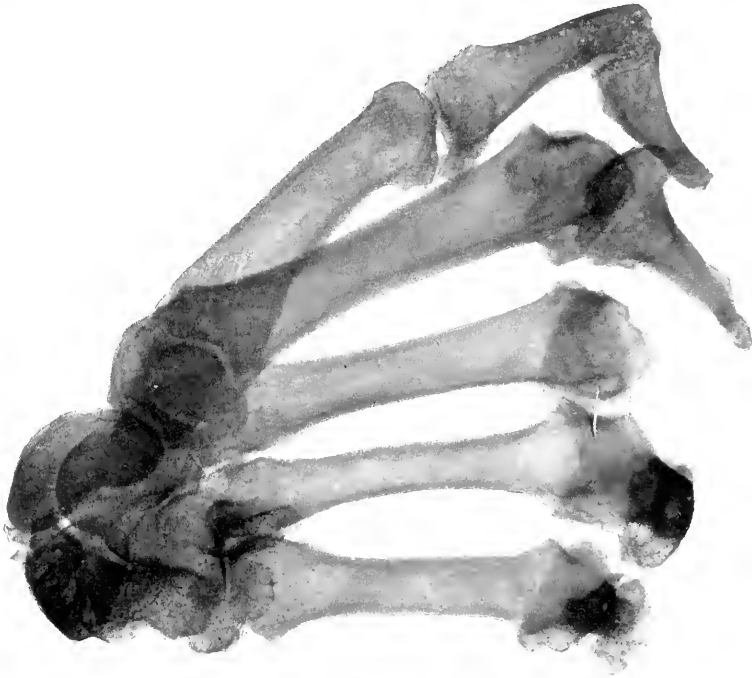


Fig. 15.—Skiagraph: same as Fig. 2.

partly grown together and have rough surfaces which, to some extent, is due to a deposit of osteophytes at the articular ends (chronic deforming arthritis). All of the metatarsal bones are much changed and atrophic, especially at the anterior ends, which are pointed, almost awl-shaped, with their heads missing. The phalanges are also atrophic and pointed anteriorly, especially in the first three toes.

- Os metatarsi I, 1.5 cm. long, with one pointed phalanx.
- Os metatarsi II, 2 cm. long, with two, thin, pointed, crooked phalanges.
- Os metatarsi III, 3 cm. long, with two atrophic phalanges.
- Os metatarsi IV, 3.2 cm. long.
- Os metatarsi V, 6.2 cm. long, about normal length.

SPECIMEN 12.—Atrophy of the tarsus with joint affections. Typical concentric atrophy of third, fourth and fifth metatarsal bones (Fig. 13). The right foot with joints and tendons from a case of leprosy of the smooth variety. The foot is a good example of the joint affection so frequently encountered in leprosy, and also presents some atrophy of the metatarsal bones. The ankle-joint is the seat of severe arthritis with marked dilatation of the joint cavity and proliferation of the synovial membrane. The tarsal bones show marked changes, consisting both in atrophy and proliferation of bone, particularly in the vicinity of the

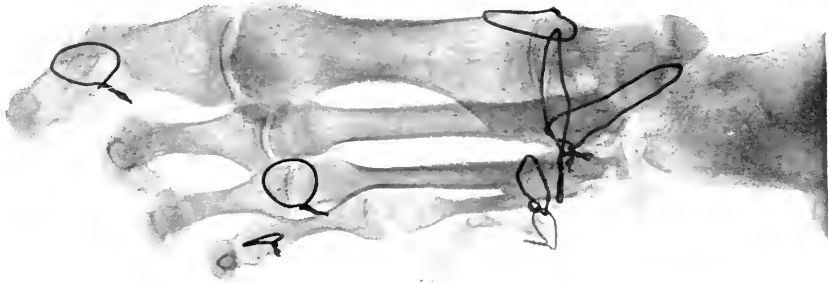


Fig. 16.—Skiagraph: same as Fig. 5.

joint. The talus is deformed, its body particularly being atrophic and reduced to a flat, bony plate. For this reason the lower end of the tibia has pressed into the tarsus. Of the os navicularis, only narrow rims externally and internally remain, which are united by a lamellar central portion. The cuneiform bones are barely demonstrable, merely formed by irregular pieces of bone fused with the first three metatarsal bones. The cuboid is atrophic, deformed, and entirely

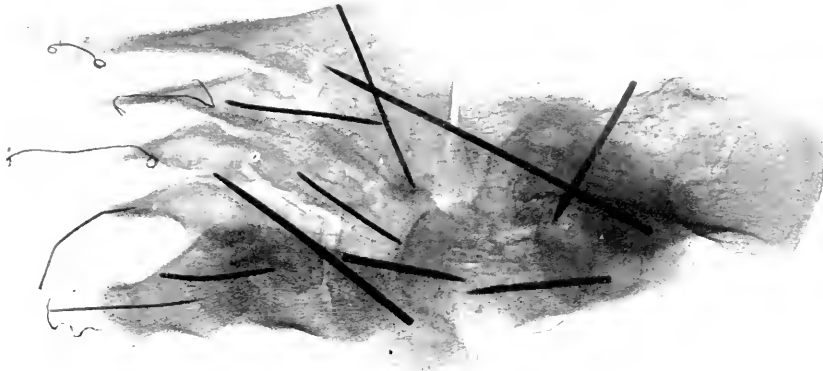


Fig. 17.—Skiagraph: same as Fig. 6.

fused with the calcaneum. On account of these severe changes in the tarsus the foot has sunken down and is in pronounced valgus position. The metatarsal bones and phalanges are somewhat atrophic, especially those of the fourth and fifth toes.

Os metatarsi I, 6 cm. long; Phalanx I, 2.8 cm.; Phalanx II, 2.5 cm.

Os metatarsi II, 6.5 cm.; Phalanx I, 3 cm.; Phalanx II, 1.8 cm.; Phalanx III, 1.4 cm.

Os metatarsi III, 5.8 cm.; Phalanx I, 2.4 cm.; Phalanx II, 1.6 cm.; Phalanx III, 1.6 cm.

Os metatarsi IV, 5.3 cm.; Phalanx I, 2.8 cm.; Phalanx II, 1 cm.; Phalanx III, 1.4 cm.

Os metatarsi V, 5.5 cm.; Phalanx I, 2 cm.; last two phalanges rudimentary.

The third and fourth metatarsal bones are fused at their base, somewhat pointed anteriorly, and flattened from side to side. Seen from above they appear as sharp edges. Also the fifth metatarsal bone is thin, and atrophic anteriorly. The phalanges on the whole are fairly normal.



Fig. 18.—Skiagraph; same as Fig. 7.



Fig. 19.—Skiagraph; same as Fig. 8.

I shall first give a collective description of the osseous changes although the illustrations convey the best idea of them.

There is an atrophy of the bones of the hands and feet which may proceed to such a degree that certain bones finally entirely disappear.



The atrophy principally affects the most distal bones, the phalanges, metacarpals, and metatarsals: it is little pronounced in the tarsus and carpus. The bones may atrophy in their entirety, though sometimes more so in the shaft, and become thin and brittle, but their shape is preserved. This variety resembles the so-called atrophy of disuse, though the bones generally are somewhat decreased in size. In the more characteristic form the atrophy is concentric and chiefly involves the most peripheral parts of the phalanges, metacarpal, and metatarsal bones. These bones become considerably shorter than normal, taper anteriorly in a cone-like manner, and may become awl-shaped; or the atrophy is most pronounced on the sides, so that the bones become plate-like with sharp edges above and below. The distal heads of the metacarpal and metatarsal bones usually

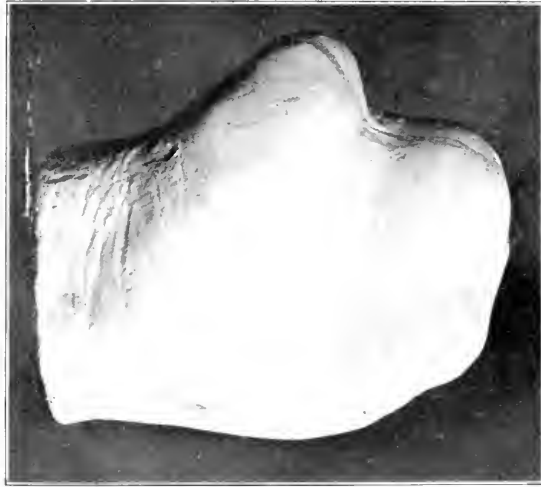


Fig. 20.—Cast of left hand; *lepra mutilans*.

disappear, while at their base the bones preserve their usual width and thickness. The surface is generally smooth. The shortening of the metacarpal and metatarsal bones may be very considerable and most pronounced either in those on the outside or those on the inside. It may be so marked that the length is only half the normal one, or even less (Specimen 6). The phalanges atrophy in a similar manner, become very thin, pointed anteriorly, and porous. Finally only disconnected remnants are left which ultimately may be entirely absorbed so that the toes become shapeless lumps without any bony framework. Our specimens illustrate this condition very well.

In the joints, various changes are also seen, on the whole resembling those of arthritis deformans. Especially in the joints of the tarsus,

we see a form of chronic inflammation of the joint-capsules with the picture of pronounced, proliferating synovitis and serous effusion (Specimen 12); at the same time, the articular ends show changes, such as atrophy of cartilage and bone, or proliferative alterations in the form of nodular projections, osteophytes, etc. The osseous substance, as a whole, in most cases is the seat of marked osteoporosis. The tarsal bones become brittle and often are squeezed together to form thin plates of bone. If the tarsus is the principal seat of atrophy, the whole foot may sink down in a pronounced valgus position. Similar signs of chronic joint disease are seen in atrophic, leprosy hands, but less frequently and less prominently.



Fig. 21.—Cast of left hand; *lepra mutilans*.

The question arises whether this peculiar bone atrophy is specific, and directly due to leprosy neuritis, or if it can be satisfactorily explained in some other manner.

In the first place it must be emphasized that these atrophies are not due to external inflammation. In other words, they do not belong to the ordinary forms of *lepra mutilans* dependent on ulceration ("mal perforant") and chronic suppuration, extending to the bones and joints, accompanied by secondary destruction of bone. As shown by the specimens, it is true that in addition to typical atrophy of bone we may also find forms of chronic inflammation which lead to extensive destruction (Specimens 4, 9, and 10), but the inflammation and the necrosis of bone have no

peculiar characteristics and may easily be recognized. They are also found in localities where there is no atrophy, and may be found wanting in the presence of typical concentric atrophy. This mode of explanation must, therefore, be excluded.

Nor can we be dealing with pure atrophy of disuse, as we then would expect to find all the bones of the foot atrophic and, what is most important, the atrophy in individual bones ought to be evenly distributed, not limited to certain parts. One would expect an anatomic picture similar to that seen in paralyzed limbs, for instance, after an attack of acute poliomyelitis. But this is not the case. In paralyzed limbs the bones usually retain their shape and ordinary size, but merely become brittle and osteoporotic, while circumscribed atrophy such as here described is



Fig. 22.—Cast of left hand: lepra mutilans.

entirely absent. It is another matter that disuse may play a considerable rôle in the development of atrophy.

Finally, it might be maintained that the atrophy might depend on genuine, specific, leprous osteomyelitis and periostitis. Lepra bacilli and leprous granulation-tissue in the osseous system have been demonstrated chiefly by Hirschberg and Biehler<sup>3</sup> and, in that case, it might be supposed that absorption of bone might result in atrophy. *A priori*, the objection could be made that in such a case concentric atrophy would be less likely to occur than the destruction of bone similar to that seen in tuberculosis

3. Hirschberg and Biehler: Lepra der Knochen. Dermat. Ztschr., 1909.

and syphilis. But skiagraphs taken of all of our cases show that there is no trace of such central lepromata or of any periostitis. This has already been pointed out by Deycke,<sup>4</sup> who also studied skiagraphs of leprosy bones. He also could demonstrate a peripheral atrophy without reactive changes, but he had no opportunity to make anatomic studies of the skeletons of the hands and feet, or to make histologic examinations.

The microscopic studies made to clear up this question, which were especially thorough in the case of Specimen 12, argue against the position that we are dealing with results of leprosy inflammation. Thus in speci-



Fig. 23.—Cast of right hand: lepra mutilans.

mens of atrophic toes, we find small pieces of bone with uneven surfaces containing osteoclasts in the depressions, but no leprosy osteomyelitis or periostitis could be demonstrated and no leprosy bacilli were found.

Therefore, no weight can be given to any of these objections. There is no good reason for doubting that this bone atrophy is really of neurotrophic origin, and everything seems to point to leprosy interstitial neuritis as the cause. As has been strongly contended by H. P. Lie,<sup>5</sup> it

4. Deycke: Knochenveränderungen bei Lepra nervorum in Roentgenograph, Fortschr. a. de Geb. d. Roentgenstrahlen. ix.

5. Lie, H. P.: Lepra im Rückenmark und den peripheren Nerven., Vienna and Leipzig, Wilhelm Braumüller, 1904.

must be maintained that the trophoneurotic changes are associated with advanced leprous neuritis of the mixed nerves, and not with a definite form of the disease, or with particular lesions of the central nervous system, or certain nerves.

In this connection, it must be remembered that similar concentric atrophy of the toes has been described as following nerve lesions of various kinds, such as gunshot wounds, causing destruction of peripheral nerves, in which case the atrophy was characterized by the toes being shorter and more pointed at the ends just as we see in characteristic leprous bone atrophy.



Fig. 24.—Cast of right foot: *lepra mutilans*.

We must also consider the cutaneous changes occurring in leprous fingers and toes. The skin becomes thin, atrophic, smooth and glistening ("glossy skin"), with atrophy of epidermis, cutis and subcutaneous tissues and with disappearance of glands and loss of hair. It has been noted in our cases that the skin finally has become scar-like and inelastic. The nails also undergo changes as they cease to grow and fall off, or become corrugated, rough, and chipped, or greatly thickened and nodular. It may be generally known, as has been shown by Hansen and Looft,<sup>6</sup> that these cutaneous changes are due to leprous neuritis and are tropho-

6. Hansen and Looft: *Die Lepra vom klinischen und pathologisch-anatomischen Standpunkte*. Biblioth. med. int., 1894, ii.

neurotic in nature and comparable to the concentric atrophy of bones. As is well known, analogous changes in the skin may follow lesions of peripheral nerves.

The question arises whether the explanation of this characteristic atrophy of bone should be looked for in special trophic nerves. Aside from the fact that these nerves are still entirely hypothetical, at least not proved experimentally, it must be sufficient to recall the influence exerted by all forms of nerves, motor, sensory and vasomotor, on tissues and organs. As the leprous neuritis involves all nerves without selection, it must be supposed that all forms of nerve fibers suffer from the chronic inflammation and that this will express itself in loss or alteration of the influence normally exerted by the nervous system on nutrition. This must be considered sufficient explanation; in other words, the leprous,



Fig. 25.—Cast of left foot; lepra mutilans.

trophoneurotic bone-atrophy does not require the assumption of the existence of trophic nerves.<sup>7</sup>

When we study histologic specimens of chronic interstitial leprous neuritis and note the marked alterations in the nerves, we readily appreciate the influence on the tissues exerted by such chronic inflammation with progressive degeneration and atrophy of nerve fibers going on for many years, and will not hesitate to look upon atrophy of the osseous system as a result.

As the opportunities for anatomic study of leprous neuritis is not as good elsewhere as in Norway, where there still is considerable, though

7. In this connection the reader is again referred to my previously mentioned work, *Om. path. an forandringer af neurotrofisk oprindelse*, 1900.

rapidly decreasing leprosy, I shall briefly relate a recent case of *lepra mutilans* with marked deformities, especially of the hands.

The case was that of a woman 72 years old, who was treated for leprosy during the last twenty-one years of her life in the dermatologic ward of the government hospital in Christiania. The onset was a few years before admittance to the hospital with anesthetic area and later cutaneous nodules on the back, face and particularly the dorsum of the hands and forearms. Gradually *lepra mutilans* with considerable deformity of the hands developed. Before death marasmus had set in and the patient also had developed leprosy inflammation of the larynx, pharynx, and mouth. The necropsy revealed changes in all the nerves examined of the right forearm and hand, especially thickening of the nerves, which increased towards the wrist in the case of the radial and median nerves



Fig. 26.—Left hand: *lepra mutilans*.

but which was most marked at the elbow in the case of the ulnar nerve. The nerves were also firm and fibrous, and, in the case of the distal part of the radial nerve, adherent to the surrounding tissues, and some of them, especially the radial nerve, contained brown or yellowish-brown deposits ("brown bodies," i. e., large heaps of bacilli). The histologic findings are as follows:

The median nerve near the wrist showed concentric thickening of the perineurium of each nerve bundle and slight lymphocytic infiltration; also increased interstitial tissue within the bundle, i. e., endoneuritis. There was marked thickening of the endoneurium in which, only here and there, few and partly atrophic nerve fibers were seen. There was marked round-cell infiltration of the ulnar nerve at the wrist. The interstitial tissue was increased and almost no

nerve fibers were demonstrable. Scattered in this granulation-tissue, there were numerous heaps of bacilli which stained red and were generally intracellular. In the radial nerve near the wrist there was proliferating connective tissue without nerve fibers with scanty lymphocytic infiltration, and exceedingly numerous, and large heaps of bacilli generally arranged longitudinally and located intracellularly.

May the articular changes described also be looked on as genuine trophoneurotic affections? This is considerably more doubtful. On account of their whole appearance they are analogous to the arthropathies accompanying certain diseases of the brain and cord, such as *tabes dorsalis* and *syringomyelia*. It is especially to the credit of Charcot to have called attention to them and to have pointed out that the arthropathies



Fig. 27.—Right hand: *lepra mutilans*.

are specific, trophic phenomena dependent on a direct nervous influence exerted by disease of the central nervous system, particularly the anterior grey horns of the cord. H. Heiberg also seems to have shared this opinion.

The findings, however, particularly those in the cord, on which Charcot and others based their hypothesis, have not been confirmed by other observers. For this reason the condition of the peripheral nerves has been looked to for explanation, and in the case of leprosy the leprous neuritis.

The question arises whether it is not more natural and correct to consider these arthropathies, and particularly the joint affections of



leprosy, as merely indirectly caused by the nervous disease. In the case of the leprous arthropathies, we must bear in mind the considerable degree of muscular atrophy produced by the neuritis which renders the joints more lax and the movements ataxic. The development of arthropathies is further favored by the condition of the bones which become brittle, osteoporotic, and deformed and easily give way to pressure and trauma of any kind. The existing analgesia and anesthesia are also of importance. The sensory nerves supplying the joint-capsules and ends of the bones are affected so that the ordinary sensation produced by the abnormal position of the joints is lost, which predisposes to ataxic movements and anatomic changes. The reflex influence of the centripetal nerves on the normal nutrition of the tissues is lost, and this also exerts its influence.

All these factors are of importance and by their indirect influence on the joints may result in the articular affections described, without it being necessary to look for the explanation in a special trophoneurotic influence.

University of Christiania.

## SERUM-THERAPY IN PURPURA HEMORRHAGICA

WITH REPORT OF A CASE

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Extensive as the literature of purpura is, the bulk of its discussion, in later years at least, is given over to pathology and to classification, while the treatment, especially of the severer forms, ambling through many diverse paths, is still far from satisfying; and must remain unsatisfactory no doubt, until its etiology has passed from the domain of interesting speculation to that of empirical fact. In view of the increasing interest in serum-therapy, and because its use has been advocated mainly in hemophilia, it has seemed justifiable to report the following case.

A brief modern history of the treatment of purpura may serve, if only by contrast, to heighten the striking effects recently obtained in some cases through the use of serum. David King, Jr., in his Fiske Prize-Essay (1836) gave the following summary of the best methods then in use:

1. Blood-letting was the great remedy in adults.
2. Nitrate of potash, acetate of lead, warm baths and turpentine were the favorite agents.
3. Mercurial purgatives were given to "restore the hepatic secretions."
4. A generous dietary, including wine, iron, and acids to "raise the vital energies" was given.

Some forty years later the fluidextract of ergot<sup>1</sup> became highly recommended; then in rapid succession pleas were made for the salicylates, acetanilid, hamamelis, the perchlorid and sesquichlorid of iron,<sup>2</sup> calcium chlorid, sodium phenolsulphonate,<sup>3</sup> and arsenic; while a small host of lesser remedies still linger by their mere inertia. Turpentine has long enjoyed prime favor. The dosage has varied from minimum to maximum, Eustace Smith<sup>4</sup> giving two to four drams in the morning, accompanied by a generous amount of castor oil. It acts thus as an aperient, and is not sufficiently absorbed to injure the kidneys. In the section on

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1. Bulkley: Practitioner, Nov., 1876.

2. Weber, Leonard: New York Med. Jour., April 10, 1897.

3. Sansom: Tr. Clin. Soc., London, May 25, 1894.

4. Smith, E.: Brit. Med. Jour., May, 1908, p. 1218.

the treatment of purpura in the new Allbutt series<sup>5</sup> is the meager statement: "The hypodermic injection of fresh animal serum has been employed," all discussion of the results being omitted; while in one of the most recent and succinct studies in this country in the Osler "System,"<sup>6</sup> the treatment outlined consists of calcium lactate, Fowler's solution, carbon-dioxid baths, oil of turpentine and aromatic sulphuric acid. Serum therapy is discussed solely in the article on hemophilia.

The stimulating researches of P. Emile Weil,<sup>7</sup> probably succeeded more than any other one factor in fastening serum usage to hemophilia, largely to the neglect of other hemorrhagic states. Pigot,<sup>8</sup> however, reported a severe case of purpura treated ineffectually with the perchlorid of iron and ergotin; the patient was later cured by serum injections, receiving 250 c.c. on three consecutive days. This, I am sure, would now be thought excessive dosage.



Fig. 1.—Patient with purpura hemorrhagica.

Weil<sup>9</sup> himself in 1907 reported a series of four cases of hemorrhage from widely differing sources treated with serum. The first patient coming in for febrile polyarthrititis, rapidly developed subcutaneous hemorrhages, epistaxis, and violent hematuria. She was treated effectually with intravenous injections of 15 c.c. of fresh beef-serum, and after one

5. Mackenzie, Sir Stephen: Allbutt & Rolleston's System of Medicine, vol. v, "Purpura."

6. Pratt, J. H.: In Osler's System, vol. iv, chap. xvi.

7. Weil, P. Emile: *L'hémophilie—pathogénie et sérothérapie*, Presse méd., Oct. 18, 1905; Bull. Soc. méd. d. hôp., Oct. 26, 1906; Tribune méd., Paris, Nov. 10, 1906; Soc. de chir., March 6, 1907; Rev. prat. d'obst. et de pédiat., March 1907; Tribune méd., Paris, Jan. 12, 1907.

8. Pigot: *Gaz. hebdomadaire de méd.*, Oct. 17, 1897.

9. Weil, P. E.: Tribune méd., Paris, Jan. 12, 1907.

mild relapse was discharged apparently cured. Weil seems impressed with the severity of this case.

The second on his list is interesting because of the coagulation time, which was two hours on admission, and after complete recovery was still fifty-five minutes. The third patient, one with purpura, made an uneventful recovery. In the fourth case, the clinical picture was that of the terminal stage of chronic interstitial hepatitis. The extensive hemorrhages into the skin were stopped entirely; the patient later succumbed to the intoxication attendant upon the course of his cirrhosis.

In a paper entitled "Chronic Purpura and Pernicious Anemias"<sup>9</sup> Weil discusses two advanced cases in which the severe ecchymoses, epistaxis, and hematuria were completely checked some months before the patient died from the anemia. In the second case, during a period of transient improvement which followed the injections of serum, the red



Fig. 2.—Patient with purpura hemorrhagica.

cells rose from 1,100,000 to 3,350,000. Signs of meningeal hemorrhage present in this case at the start, completely disappeared along with the cessation of the other bleedings.

In 1908 Leary<sup>10</sup> reported a series of twenty cases from Boston. In fifteen, hemorrhages had already appeared; in the other five, the serum was used as a prophylactic measure, principally in patients profoundly jaundiced in whom operative measures were found imperative. The cause of hemorrhage in this list includes cholemia, hemorrhage of the new-born, hemophilia, purpura (this case is also reported in full by Larrabee<sup>11</sup>), and a few post-operative hemorrhages, curettage, submucous resection of septum, ritual circumcision and typhoid hemorrhage. The case of circumcision proved fatal. It presented early in the series, while

10. Leary: Boston Med. and Surg. Jour., 1908, clix, 7.

11. Larrabee: Boston Med. and Surg. Jour., 1908, clix, 682.

experience was still meager, and Leary is convinced that this patient too could have been saved, if serum more frequently and in larger doses had been given.

As to the kind of serum to be used, Weil suggests that rabbit, beef, antidiphtheritic or human serum is serviceable; but the beef is least desirable, as constitutional reactions (fever, chills, cyanosis and vomiting) are more pronounced with it than with any other. The dosage in general use is: 15 c.c. intravenous or 30 c.c. subcutaneously for an adult, while half the amount usually suffices for a child. The dose may be repeated in two days, and should be given at any rate in ten to prevent anaphylaxis. Serum disease appeared but once in Leary's twenty cases, and was then more annoying than serious. The serum should be fresh, certainly not more than fourteen days old, and the fresher specimens prove by far the more efficacious.

#### REPORT OF CASE

*Patient.*—The present case, which may be added to those already reported, is that of an adult woman who entered the medical wards of St. Luke's Hospital<sup>12</sup> on May 11, 1908, on the service of Dr. Theodore C. Janeway. Chief complaint: Pain in the region of the bladder; hemorrhages under the skin.

*Present Illness.*—Three days ago the right wrist became swollen and painful and a hemorrhagic spot appeared over the head of the ulna. The pain rapidly grew worse and other joints began successively to be painful. Meanwhile the patient had chilly sensations, fever, and crops of petechial spots on various parts. The pain disappeared in about thirty-six hours except for a severe burning and aching in the bladder region. This has persisted till the present time, and is not influenced by urination. The urine is dark-brown in color and looked to the patient as though it contained blood.

*History.*—Ten years ago, after exposure to cold, the patient had a profuse bleeding from the gums: they were spongy and purple. A day later small petechial spots appeared on the body. She recovered after two weeks. At times she has bruises on her body which she cannot account for. Family history is irrelevant.

*Physical Examination.*—Hemorrhagic spots varying in size from petechiae to the diameter of a centimeter or more cover a large part of the chest and abdomen. About the elbows, wrists and ankles, especially on the right side, are diffuse hemorrhagic areas 8 or 10 cm. in diameter. In these regions there are no petechial spots other than the larger areas. On the back of the hard palate is a small hemorrhagic patch. Herpes is present on the upper lip. The bladder is enormously distended. The right kidney is exquisitely tender to pressure, especially posteriorly. The left kidney is similarly so, but to a lesser degree. The lower poles cannot be felt. In other respects the physical state is normal. Eye-grounds show no hemorrhages.

*Clinical Notes.*—On admission, May 11, temperature was 100.2, pulse 104, respirations 24, blood-pressure 80 mm. Hg in systole. Blood examination: Red cells, 3,468,000; hemoglobin, 75 per cent.; white cells, 5,500; polymorphonuclears.

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12. St. Luke's Hospital, Med. Case No. 77436.

64 per cent.; lymphocytes, 36 per cent. Coagulation time (Brodie), 2 minutes 43 seconds. Urinalysis: Acid, 1014; albumin, 15 per cent.; no sugar; microscopic hyaline and granular casts and blood.

The patient was given an amount equal to 5,000 units of diphtheria antitoxin. As there was no serum then available, this was used as the nearest substitute. This was the precipitated antitoxin now in use by the New York Board of Health. Calcium lactate grs. xx t. i. d. was ordered rather as a routine measure.

During the next four or five days there appeared no new hemorrhages, and the stools and urine showed less and less blood. On May 17 she was given 6,400 units of the same antitoxin. Calcium lactate was stopped.

Improvement was steady and convalescence seemed well established until June 17, when the patient again complained of sharp pains in the bladder region. No ecchymoses were found, however, and she seemed to progress until June 30. This morning she was nauseated and vomited. There were several small ecchymotic spots on the legs. Stools fluid and black. They contained blood. The urine contained blood also. The temperature rose abruptly to 102.3 F.

The patient was given 10 c.c. fresh horse-serum subcutaneously. This time recovery was prompt and permanent.

She left the hospital July 15 in excellent condition, and in a recent interview says she is still, after ten months, enjoying perfect health.

I desire to express my appreciation to Dr. Janeway for the privilege of reporting the details of this case.

16 Central Park West.

## A STUDY OF CASES OF HODGKIN'S DISEASE AND CERTAIN ALLIED CONDITIONS\*

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The following observations were thought to be of value because they add to the number of reported cases of a somewhat rare disease and because I believe that they throw some light on an obscure and much-discussed subject. The report of a case of Hodgkin's disease running an acute course, the diagnosis of two other cases by the examination of lymph-nodes removed surgically, the report of a case of tuberculous lymphadenitis whose histologic appearance closely simulated that of Hodgkin's disease, and a case of Hodgkin's disease that appears to have undergone sarcomatous transformation, form a series from which, with other observations from the literature, certain well-supported conclusions may be drawn.

I shall not go into a wearying presentation of the literature, which has been reviewed most completely in the papers by Reed,<sup>1</sup> Longcope,<sup>2</sup> and Yamasaki,<sup>3</sup> and in some of the more extensive articles such as those of Paltauf<sup>4</sup> and of Sternberg,<sup>5</sup> but shall enter immediately into the presentation of the cases in the order already given.

### I. HODGKIN'S DISEASE

CASE I.—*Patient*.—A. J. W., male, single, white, aged 17, printer, born in Philadelphia, was admitted to the Bryn Mawr Hospital July 21, 1908, service of Dr. George Gerhard, where he was most carefully studied by Dr. Gerhard, Dr. Billings and Dr. E. Burvill-Holmes. Their complete and detailed report is abstracted as in the following notes:

*Chief Complaint*.—Persistent bleeding from the nose.

*Family History*.—Parents living and well; 2 brothers and 3 sisters living and well; one brother died in childhood. No history of tuberculosis except that the patient's mother five years ago had what appeared to be pulmonary hemorrhages, but repeated examination by the physicians at the Phipps' Institute have failed

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\* From the McManes Laboratory of Pathology, University of Pennsylvania; read before the Pathological Society, Philadelphia, March 24, 1910.

1. Reed: Johns Hopkins Hosp. Rep., 1902, x, 133.

2. Longcope: Bull. Ayer Clin. Lab. of the Pennsylvania Hosp., 1903, i, 4.

3. Yamasaki: Ztschr. f. Heilk., 1904, xxv, Abt. f. path. Anat., 269.

4. Paltauf: Ergebn. d. allg. Path. u. path. Anat. (Lubarsch and Ostertag), 1896, iii, 652.

5. Sternberg: Ztschr. f. Heilk., 1898, xix, 21; Pathologie der Primärerkrankungen des lymphatischen und hämatopoëtischen Apparatus, etc., Wiesbaden, 1905.

to show the least trace of a lesion; she has had no repetition of the hemorrhages and appears to be perfectly well. There is no family history of hemophilia except that the father formerly had frequent attacks of epistaxis, but the attacks were always stopped readily. No history of heart or kidney disease except that the patient's maternal grandfather, living at the age of 65, is said to have heart and kidney trouble. No history of neoplasm.

*Personal History.*—Patient has had measles but no other children's diseases. Four years ago had a mild attack of typhoid fever, and has been troubled with frontal headaches more or less ever since. He thinks that this is due to an ocular condition, as an oculist told him that he should wear glasses. Otherwise he has always been healthy. He is small for his age, height 5 feet 3 inches, and in the spring of this year his weight was 113 pounds. He attended school until three years ago and then entered a department store as a cash-boy. He then spent six months learning the plumbing trade and for a considerable time has been a printer's apprentice. The hours were long, the work has been hard, sometimes extending into the night. He formerly smoked a pipe to considerable extent and cigarettes occasionally, but has not smoked for several months. He does not use alcohol and denies all history of venereal infection.

*Present Illness.*—Six months ago he "strained himself" lifting a bale of hay weighing 165 pounds. Shortly afterward he had severe pain in the stomach which lasted for about ten minutes, and a few days later he noted a swelling in his right axilla which he attributed to the strain. He says that it grew rapidly so that within a week the swelling had attained its present size. He had not noticed swellings in other places. Three months ago he had a sudden and severe nose-bleed which lasted for three hours, and since that time the bleeding has occurred frequently, sometimes small in amount, sometimes very severe. Four weeks ago he noticed a number of purpuric spots on his legs, and within the past week the bleeding has been so severe that he sought admission to the hospital.

*First Examination.*—A lad who appears to be about 15 years of age, very pallid and apparently very weak. He lies quietly with no objective symptoms of pain. Purpuric spots in small numbers over chest, back and shoulders.

*Head:* Hair is dark brown, thick and firm. Eyes show equal pupils which react readily to light and accommodation. There is no nystagmus; the ocular muscles are normal and conjunctiva is pale. Nose shows large nostrils which do not play and show no signs of bleeding. The tongue is moist, shows a dark brown coating, but no fissures nor tremor. Gums are anemic, but bleed on pressure. The teeth are fair, but the breath has a foul odor. The lips and mucous membranes are very pallid. The face shows a few small purpuric spots.

*Chest:* Typical chicken-breast with marked emaciation. Clavicles not especially prominent; expansion excellent and equal on both sides; no bulging except at the costochondral junction at the lower border of the sternum. Over the precordium a slight thrill which extends upward toward the left.

*Lungs:* Breath sounds normal; vesicular throughout; resonance good, extending 4 to 5 cm. above the clavicle. No dulness or hyperresonance, and no râles.

*Heart:* Dulness from the upper border of the third rib to a point 3.5 cm. to the right of the mid-sternal line in the third interspace and 5.5 cm. to the left of the mid-sternal line over the third rib. Apex 8.5 cm. to the left of the mid-sternal line. A blowing murmur at the apex carried well over the precordium. This at times appears to be systolic, but the first sound is blurred in such a fashion as to suggest a duplication and the volume of sound is so weak as to produce a gallop rhythm.

*Abdomen:* Muscles somewhat rigid, but no distention and no abnormal amount of tympany. In the right iliac region a resistant mass, but nothing else is revealed to palpation.



Liver: Reaches from the fifth rib in the midclavicular line to the margin of the ribs. In the back it reaches to the eighth rib on the right side and to the tenth rib on the left.

Spleen: Not palpable, but percussion shows slight enlargement upward and backward. Lymph-nodes: Those in the right axilla are considerably enlarged but are discrete. Cervical and inguinal are barely palpable. No changes in other lymph-nodes. Extremities and genitalia: Negative.

TABLE 1.—BLOOD EXAMINATIONS\*

Date	R. B. C.	Hb. Per cent.	Leuk.	Poly.	Large Lymph.	Small Lymph.	Eosin.	Baz.
7, 21...	3,290,000	.....	5,600	67.2	24.4	7.6	0.8	
7, 30...	.....	.....	6,600					
8, 4...	1,900,000	33	5,000	62.8	19.2	17.6	0.4	Erythroblasts, Poikilocytosis, Basic degeneration, Anisocytosis.
8, 10...	.....	32	.....	58.4	28.8	11.6	1.2	Anisocytosis, Poikilocytosis.
8, 13...	860,000	34	4,400	59.2	22.0	18.4	0.4	
8, 20...	1,510,000	40	4,900	62.0	16.4	20.0	1.6	Anisocytosis, Poikilocytosis, Normoblasts.
8, 27...	2,350,000	49	5,800	64.8	13.6	20.0	1.6	Anisocytosis, Poikilocytosis.
9, 3...	3,200,000	44	6,200	59.6	14.0	24.6	1.2	Poikilocytosis.
9, 12...	2,350,000	45	5,600	59.2	8.0	30.0	0.8	Anisocytosis, Poikilocytosis.
9, 21...	3,090,000	36	5,200	54.8	34.4	10.0	0.8	
9, 26...	3,400,000	42	6,200	65.0	8.0	25.0	2.0	
10, 5...	3,130,000	47	5,000	66.4	19.2	11.6	2.8	Anisocytosis, Poikilocytosis.
10, 10...	.....	.....	7,800					
10, 13...	2,940,000	41	4,000	56.8	18.8	23.6	0.8	Poikilocytosis.
10, 20...	2,730,000	38	4,000	56.0	24.4	11.2	0.4	Anisocytosis, Poikilocytosis.
11, 19...	1,480,000	26	4,600	80.8	5.6	13.6	0	Anisocytosis, Poikilocytosis.
11, 25...	1,020,000	18	3,000	54.4	26.0	26.4	3.2	
12, 1...	.....	12						

\* Blood culture was negative.

The feces examined October 6 showed a small amount of blood, but no ova or parasites.

The Moro tuberculin test (cutaneous), made August 22, was negative, no rash appearing in forty-eight hours.

Patient's temperature on admission was 98.8 and it continued along the normal line until twelve days after admission, when a drop down to 95.6 was followed by a rise to 102 within a very short time. The pulse, which had been run-

ning about 80 to the minute, rose to 101, and the respirations gradually rose from 20 to 24. This elevation of temperature gradually subsided over the course of five days, but it was accompanied by considerable enlargement of the lymph-nodes and the appearance of blood in the urine. After this time the temperature remained close to normal except that there was a slight rise each evening, the entire variance amounting to about two degrees, and never exceeding 100 Fahrenheit except on three apparently accidental occasions. The pulse varied between 80 and 100, being more frequently 80 than 100. Respirations varied between 20 and 24.

During the time in the hospital numerous hemorrhages occurred, particularly from the nose, and blood was occasionally found in the urine.

On August 27 the axillary nodes underwent a sudden moderate enlargement without any accompanying temperature rise or pulse acceleration. On August 15 the patient was placed on a special prescription of citrate of iron, sodium cacodylate and sodium glycerophosphate, which was administered hypodermically, apparently with fairly good results. Throughout the time of his stay in the hospital crops of purpuric spots appeared from time to time.

TABLE 2.—URINE

Date	Clear.	Color.	Ppt.	Sp. Gr.	React.	Urea, Per cent.	Chlor' ds.	Blood.	Indican.	Diazo.	Alb., Per cent.	Sugar.	Microscopic.
7, 21.	Turbid..	Pale amber.	Flocculent.	1010	Acid	1	Normal.	None....	Moderate.	Neg.	0	0	Leucocytes, Epithelia, Bacteria.
9, 15.	Clear....	Amber....	.....	1018	Acid	.....	.....	.....	.....	.....	.....	.....	.....
9, 23.	Turbid..	Straw....	.....	1010	Acid	.....	.....	None....	Faint trace.	.....	0.2	0	Bacteria.
10, 5.	Turbid..	Amber....	.....	1020	Acid.	.....	.....	Present.	Faint trace.	.....	+	0	Erythrocytes.
11, 20.	.....	.....	.....	1005	Acid.	.....	.....	Neg....	Neg....	Neg.	0	0	Uric acid crystals, Epithelia.

On October 22 the patient found that he was gradually getting worse and asked to be discharged. This request was complied with and on November 19 he was readmitted, for the same complaint, and giving the same history.

*Later Examination.*—Physical examination at this time showed no variation from that of his first admission. X-ray pictures showed nothing of any moment and Dr. Carpenter was asked to examine the eyes, which he did on the 22d, finding a bilateral hemorrhagic retinitis with vitreous hemorrhages, and with no optic neuritis. On the 26th he repeated the examination, finding a hemorrhagic neuroretinitis with signs of obstruction in central venous circulation.

Dr. Woods on November 27 made a neurologic examination and found that there was no sensory disturbance except for vague numbness in the lower extremities. The knee-jerks were slightly increased; ankle-clonus not present; plantar reflex normal. There was an occasional jerking of the lower limbs which was involuntary, but there was no spasticity and the patient's strength was fair.

On December 1, the patient, after having been semi-conscious and delirious for several days, died. On this day his hemoglobin had fallen as low as 12 per cent. Dr. Holmes states personally that at one time the hemoglobin was as low as 9 per cent., although the record was not made.

## AUTOPSY

The autopsy was performed by Dr. Holmes and a synopsis of his findings is appended.

*General Appearance.*—Body of a young male; emaciation is slight; skin is of a pale yellow-white color. Distributed over the body petechial spots are demonstrable. Most of these are discrete but in certain areas they are confluent. This latter condition is particularly well marked in the right axilla where they form a circumscribed area, purple in color, about 7 cm. in diameter. The petechiae are purple in color generally and vary in size from a pin-head to three times that size. Slight edema of the subcutaneous tissues is present. A fair amount of fat, pale yellow in color. Muscles are pale in color and somewhat softer in texture than normal.

*Viscera.*—Lungs show slight edema at both bases; are generally pale in color, otherwise normal. Right ventricle of heart is slightly dilated; the muscularis is firm but pale in color. Valves are apparently normal. The right heart contains much blood which is still fluid and pale in color, appreciably paler than normal. Liver is not enlarged; on section is pale in color but firm. Spleen is not enlarged, weighing 160 gm. It appears normal macroscopically. Kidneys are enlarged and softer than normal; striae are apparent; cortex is slightly if at all enlarged. Capsule strips readily; the parenchyma is pale in color. Bladder shows nothing abnormal.

*Lymph-Nodes.*—Nowhere except in the right axilla are the lymph-nodes enlarged. At the latter site seven nodes are found which are markedly enlarged. These vary from the size of a hazel-nut to that of a large English walnut. They are apparently abnormally fibrous.

*Pathologic Diagnosis.*—Slight edema of the lungs; cloudy swelling of the liver; subacute parenchymatous nephritis; lymphadenitis of the right axillary nodes.

## HISTOLOGIC EXAMINATION

Sections of the liver, spleen and lymph-node were referred to me for histologic examination and my report follows:

*Liver.*—Capsule not present. Capsule of Glisson shows slight overgrowth of old connective tissue. The capsular veins are of normal thickness but are slightly distended with blood. The arteries show an apparent increase in thickness of the walls in comparison to caliber. The bile-ducts are normal in number and character. The parenchyma shows a normal cell arrangement, but the individual cells, while only moderately swollen and very sharply outlined, show marked granularity of the protoplasm, the intervening vacuolization suggesting the presence of minute fat globules. The degeneration is somewhat more marked centrally in the lobule than peripherally. The nuclei for the most part are well stained, sharply outlined and vesicular, with the chromatin showing a tendency to deposit itself as droplets toward the nuclear membrane. The nuclei show moderate variations in size, the smaller ones being less vesicular than the larger ones. A few nuclei show well-marked fading and obscuration and some few of the cells show no nuclei whatever. The central veins are filled with blood, the corpuscles being crowded into the adjacent capillaries and compressing the surrounding cells. Numerous moderately large granules of golden brown translucent pigment are scattered through the section, sometimes intracellular, sometimes extracellular.

*Spleen.*—The capsule shows a slight thickening and is of normal density, the same being true of the trabeculae. The follicles are present in normal numbers, somewhat enlarged and poorly outlined. The cells of the follicles show an admixture, in small numbers, of endothelial cells with large vesicular nuclei and rich protoplasm. A moderate overgrowth of supporting tissue is also seen in these

areas. The central arteries are apparently normal. The pulp shows moderate congestion. Here and there are numerous areas in which a fine fibrillar network and many deeply stained spindle-shaped nuclei indicate a connective tissue overgrowth. Marked endothelial cell proliferation is noted throughout the pulp and some of the cells are of enormous size although still mononuclear. Red blood corpuscles are numerous. There are also present numbers of mononuclear cells with deeply staining, relatively small eccentrically placed nuclei, whose chromatin is arranged as a solid mass. The protoplasm is rich, markedly acidophilic and non-granular. They suggest nucleated red cells, but the protoplasm takes the eosin in a more intense manner than the erythrocytes, so that they are better classified as acidophilic plasma cells. Coarse translucent golden-brown granules, probably of hemosiderin, form numerous clumps in the pulp.

*Lymph-Node*.—Capsule is somewhat thickened and shows as a mass of dense old connective tissue. A very well-marked fibrosis is visible throughout the node, more especially marked toward the capsule and apparently showing slight increments in the neighborhood of blood-vessels. The pulp of the node shows no suggestion of follicular arrangement, the cells being diffusely distributed over the field. A large number of the cells are of the typical lymphoid type with relatively large deeply staining nuclei and are poor in protoplasm. About equal in number are somewhat larger mononuclear cells richer in protoplasm and with oval and circular distinctly vesicular nuclei—endothelial cells. Acidophilic plasma cells similar to those in the spleen are present in very small numbers. Mononuclear and polynuclear giant cells like those described by Reed, Longcope, and others—cells whose transverse diameter is equal to about five of the ordinary lymphoid cells—are present in large numbers. Most of these mononuclear giant cells have vesicular nuclei whose chromatin is arranged in a rather loose network; some other nuclei cells of the same size show a denser structure. The polynuclear giant cells show overlapping, comparatively small vesicular nuclei, whose chromatin is again in a loose network. The number of nuclei varies from two to about eight or ten. Pigment similar in appearance to that seen in the spleen and liver is present in relatively large amounts.

*Diagnosis*.—Cloudy swelling and hemosiderosis of liver; Hodgkin's disease of spleen and liver.

Emulsion of the lymph-node injected into a guinea-pig did not produce tuberculosis, and specimens of lymph-node stained for tubercle bacilli were negative.

CASE 2.—*Patient*.—A. B., female, white, aged 28. The specimens were referred to the laboratory by a correspondent who states that the patient had lymphatic enlargement six years ago which almost completely subsided. Five years ago she had an attack of acute articular rheumatism and since then has had occasional joint pains. During the last thirteen months she has had paroxysmal pain of about one hour's duration in knees, hips and thighs, occurring several times daily. The pains recently involved the back, hips and iliac fossæ. Two months ago she detected a hard growth in the inguinal region, which has enlarged rapidly. Exploratory operation showed much enlarged ovaries which were removed, and at the same time one of the inguinal lymph-nodes was taken for examination.

These were examined in this laboratory and a report of spindle-cell sarcoma of the ovary and Hodgkin's disease of the lymph-node submitted.

#### HISTOLOGIC EXAMINATION

Histologically, the lymph-node showed well-marked fibrosis of the capsule and interstitial supporting tissue. The follicles and cords and sinuses show complete obliteration, the mass, however, being richly cellular. There are found large numbers of lymphocytes of the usual type. In addition there are a few endothelial cells and fewer plasma cells. Careful examination of the slide shows practically

no eosinophils. Scattered throughout, attaining fairly large numbers, are giant cells of polynuclear type, and, to a very much less degree, of mononuclear variety. The polynuclear forms are rich in protoplasm and show from four to six nuclei, which are vesicular and overlapping. The mononuclear forms show a fairly rich protoplasm with a single large vesicular nucleus. There is no pigment present in the section. Careful examination for tubercle bacilli is negative.

*Diagnosis.*—Hodgkin's disease.

A letter from the patient's physician confirms the diagnosis of Hodgkin's as the enlargement of the nodes extended and included all the superficial nodes and those of the pelvic and abdominal cavities. The patient developed a high grade of anemia. A trip to Colorado relieved her considerably and at the present time she seems much improved.

CASE 3.—*Patient.*—M. S., female, white, single, aged 18, native of Pennsylvania. The axillary lymph-nodes were referred to this laboratory through the State Laboratory by Dr. J. W. Ellenberger of Harrisburg, who states that the patient had been treated for rheumatism for six months before he saw her. At that time she complained of pain in the right shoulder and appeared to be very anemic, although not emaciated. Examination showed a mass of enlarged lymph-nodes under the right clavicle. The patient was operated on and a mass of nodes large enough to fill both hands was removed, being regarded by the operator as either sarcomatous or tuberculous. The patient was much relieved and several months afterwards is said to have gained considerably in flesh and strength. The histologic examination made by me is appended.

#### HISTOLOGIC EXAMINATION

Two sections of lymph-node showing essentially the same features. The capsule is of about normal thickness and appears to extend around the entire node. The fibrous tissue in parts shows a loose arrangement and throughout shows moderate infiltration with lymphocytes. The node itself shows complete obliteration of the follicles and sinuses, no suggestion of these structures remaining whatever. Finer examination of the node shows that there is a great excess of fibrillar connective tissue present, separating the cells throughout the node by its fine network. The cells for the most part are small, deeply stained lymphocytes, but in addition there are numerous cells present of the type of endothelial cells with large vesicular nuclei and fairly rich protoplasm. A few plasma cells are present and a moderate number of large mononuclear giant cells with large vesicular nuclei and a relatively rich protoplasm; these cells being four, five, or six times the size of a lymphocyte in transverse diameter. There also are present a very few polynuclear giant cells showing the same type of nucleus, somewhat smaller and overlying one another. Examination with the oil-immersion lens discloses the presence of one typical eosinophil. The connective tissue nuclei are for the most part of a young type showing as oval, and spindle-shaped vesicular nuclear masses. Careful examination shows the presence of a small amount of finely granular, dark brown pigment. Vascularization is not very rich, the vessels showing distinct walls—walls that do not seem to be made up of cells forming the node proper, but are rather distinctively endothelial and smooth muscle cells. Examination of one of the nodes with the oil-immersion lens and mechanical stage fails to show tubercle bacilli.

*Diagnosis.*—Hodgkin's disease.

The diagnosis in all three cases is certainly Hodgkin's disease. The first case is peculiar in several ways. Its course is to be looked on as acute, reaching its termination in one year from the onset and although

Reed claims that the cases running an acute course are of doubtful nature, this case, with some others, notably that of Hirschfeld and Isaak,<sup>6</sup> leave little doubt that acute cases, though rare, may occur. The unusually well-marked features of high-grade anemia seen in the frequent epistaxis, purpuric eruptions, hemic murmur and the great reduction of erythrocytes, are exceptional features, rendered more so by the fact that the hemoglobin erythrocyte ratio is rather that of the pernicious type of anemia than of the simple secondary type common to this disease.<sup>7</sup> It might be thought that the blood condition is an essential purpura hemorrhagica, but to me the more reasonable view seems that the condition is an exaggeration of the customary anemia. The leukocyte count shows what I consider a distinct leukopenia with a well-marked increase in the combined percentages of the two forms of lymphocytes, at times the large forms predominating, at other times the small. Pinkus<sup>8</sup> holds this to be of considerable importance, but an examination of the more recent literature shows that, while a relative lymphocytosis often occurs, it is by no means essential to the diagnosis.

An added feature of interest is the fact that although Hodgkin's disease as a rule primarily affects a chain of nodes rather than a single node, thence becoming generalized,<sup>9</sup> yet in this case the process, beginning in a chain, limited itself to that chain, the involvement of the spleen apparently being very recent and inferred from the fibrosis, obscuration of follicles and well-marked eosinophilia. I do not wish to be thought of as considering eosinophilia in any sense diagnostic of Hodgkin's disease, but refer to it as being of only suggestive import. Indeed the lymph-nodes in the three preceding cases fail to show eosinophilia and although Reed, Dietrich,<sup>10</sup> Andrewes<sup>11</sup> and others attach much importance to it, the more recent opinion, as expressed by Fischer,<sup>12</sup> Longcope,<sup>2</sup> and Warnecke<sup>13</sup> would indicate that many typical cases lack this feature. That eosinophilia occurs in the lymph-nodes in other conditions such as diphtheria<sup>14</sup> and general tuberculosis not especially of the lymph-nodes<sup>15</sup>

6. Hirschfeld and Isaak: *Med. Klin.*, 1907, lli, 1580.

7. Fischer: *Deutsch. Chir.*, 1901, instalment 24a, p. 104.

8. Pinkus: *Nothnagel's spezielle Pathologie und Therapie*, 1901, viii, part 2, p. 81.

9. Kmdrat: *Wien, klin. Wchnschr.*, 1893, vi, 211, 234.

10. Dietrich: *Deutsch. med. Wchnschr.*, 1908, xxxiv, 1188.

11. Andrewes: *Tr. Path. Soc. London*, 1902, liii, 297.

12. Fischer: *Arch. klin. Chir.*, 1897, lv, 467.

13. Warnecke: *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1904, xiv, 275.

14. Councilman, Mallory and Pearce: *A Study of 220 Fatal Cases of Diphtheria*, Boston, 1901.

15. Foster: *Jour. Med. Research*, 1908, new series, xiv, 83.

is ample proof of the fact that it cannot be considered of great diagnostic importance. Such limitation to a single group of nodes is unusual but does occur, as has been reported very recently in the paper by Schottelius.<sup>16</sup>

The clinical exclusion of tuberculosis as an etiologic factor is of great importance, as will be shown later, as also is the exclusion of intestinal conditions. And it is especially noteworthy that these findings were supported by the result of the autopsy, the inoculation experiments and the negative examination for tubercle bacilli in the tissues.

Cases 2 and 3 show very well the value of removal of enlarged lymph-nodes for diagnostic purposes. Both failed to show eosinophilia in the histologic examination and both were negative for tubercle bacilli. An interesting feature of these two cases is the occurrence of pain in the adjacent nerve trunks. Patient 3 was treated for rheumatism for a long period before the enlargement of the lymph-nodes was detected, the pain subsiding after their removal, and Patient 2 had pain in the lower extremities, the enlarged nodes being in the groin, but inasmuch as there was a pelvic complication, this may have been the cause of the pain. In both cases the disease appears to be of the chronic type.

Specimens from these three patients and from Patient 5, whose case is described later on, and which is also to be looked on as a case of Hodgkin's disease, were stained by the Levaditi method in order to demonstrate, if possible, spirochetes similar to those described by Pröscher and White.<sup>17</sup> In Case 3 minute bodies about 5 microns in length were seen, which took the silver very deeply and which resembled those described by the above authors, except that they were shorter and more tightly coiled, but which I do not feel were distinctive enough to be called true spirochetes. All the other sections examined were negative, although the process of staining was identical in all four.

## II. TUBERCULOUS LYMPHADENITIS

Although it seems certain that Hodgkin himself did not recognize the distinct character of the condition that bears his name and that he probably included tuberculous lymphadenitis in his cases, yet later writers,

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16. Schottelius: *Virchow's Arch. f. path. Anat.*, 1906, clxxxv, 326.

17. White, W. C., and Pröscher, F.: *Spirochetes in Acute Lymphatic Leukemia and in Chronic Benign Lymphomatosis (Hodgkin's diseases)*, *Jour. Am. Med. Assn.*, 1907, xlix, 1115; *New York Med. Jour.*, 1908, lxxxvii, 9.

until the publication of Sternberg's work, had a much clearer conception of the difference between tuberculous lymphadenitis and Hodgkin's disease. C. Hilton-Fagge,<sup>18</sup> Pye-Smith,<sup>19</sup> Delafield,<sup>20</sup> Askanazy<sup>21</sup> and some others seem to have recognized a clear distinction between tuberculosis of the lymph-nodes and Hodgkin's disease. The appearance of Sternberg's paper, however, with the assertion that Hodgkin's disease and a peculiar form of tuberculosis of the lymphatic apparatus were identical, led to much confusion; and even although Sternberg has receded some-

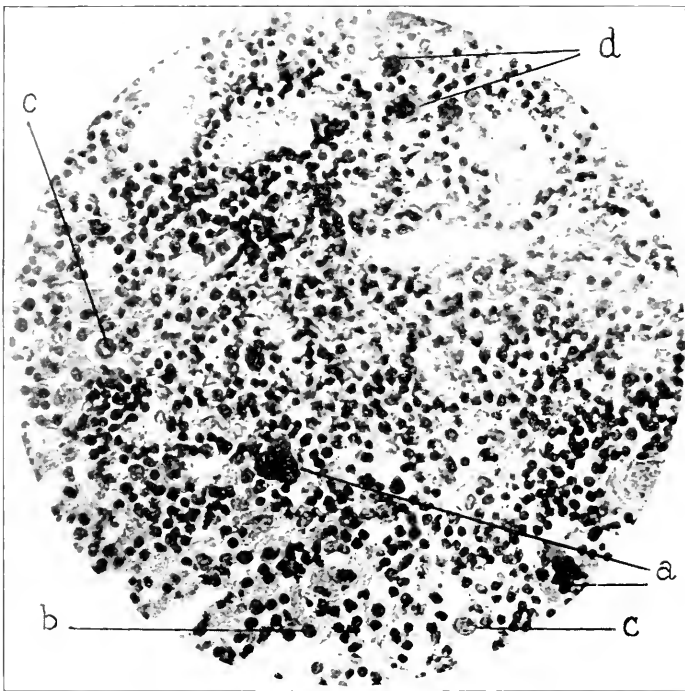


Fig. 1.—Photomicrograph of tuberculous lymph-node (Case 4), showing, at a, giant cells; at b, plasma cell; at c, endothelial cells; at d, mononuclear giant cells.

what from this original position, believing now that the peculiar tuberculosis represents an inflammation that should be separated from true pseudoleukemia,<sup>22</sup> yet several articles have appeared supporting his origi-

18. Hilton-Fagge, C.: Tr. Path. Soc. Lond., 1874, xxv, 235.

19. Pye-Smith: Tr. Path. Soc. Lond., 1875, xxvi, 202.

20. Delafield: Med. Rec., New York, 1887, xxxi, 425.

21. Askanazy: Beitr. z. path. Anat. u. z. allg. Path., 1888, iii, 411.

22. Sternberg: Verhandl. d. deutsch. path. Gesellsch., 1904, i, 129.



inal contention, notably those of Crowder,<sup>23</sup> Ferrari and Comotti,<sup>24</sup> Steinhaus,<sup>25</sup> Schur,<sup>26</sup> Türk,<sup>27</sup> and Hirschman and Stross.<sup>28</sup>

Work of numerous other writers, probably first among whom stands Clarke,<sup>29</sup> take exception to Sternberg's view. Among these must be mentioned Reed,<sup>1</sup> Butlin,<sup>30</sup> Longcope,<sup>2, 31</sup> Simmons,<sup>32</sup> Fischer,<sup>7, 12</sup> Yamasaki,<sup>3</sup> Schottelius,<sup>16</sup> MacCallum<sup>33</sup> and Duval and Howard.<sup>34</sup>

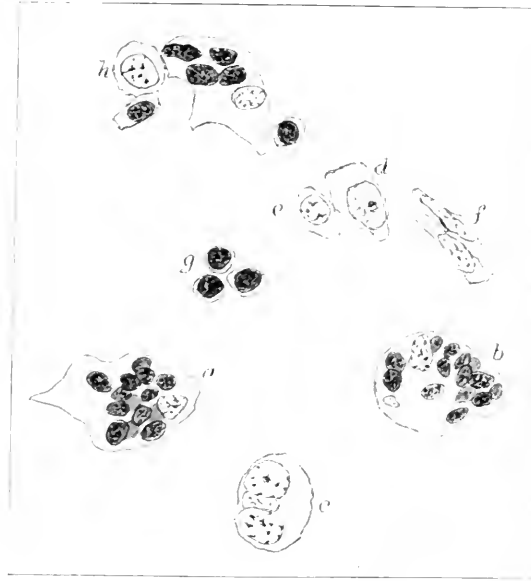


Fig. 2.—Camera lucida drawing (Spencer 1 1/2-inch oil-immersion, No. 2 ocular) showing isolated cells from tuberculous lymph-node (Case 4), the letters corresponding to references in the histologic description.

In the midst of such a strife I welcomed the finding of a single lymph-node in the following case, which shows to my mind very conclusively that a form of lymphatic tuberculosis may occur, producing

23. Crowder: *New York Med. Jour.*, 1900, lxxii, 443.
24. Ferrari and Comotti: *Wien. klin. Rundschau*, 1900, xiv, 1035.
25. Steinhaus: *Wien. klin. Wchnschr.*, 1903, xvi, 348.
26. Schur: *Wien. klin. Wchnschr.*, 1903, xvi, 123.
27. Türk: *Wien. klin. Wchnschr.*, 1903, xvi, 1073.
28. Deutsch, med. *Wchnschr.*, 1903, xxi, 365.
29. Clarke: *Brit. Med. Jour.*, 1901, ii, 701.
30. Butlin: *Tr. Path. Soc. London*, 1902, liii, 297.
31. Longcope: *Osler's Modern Medicine*, vol. vi.
32. Simmons: *Jour. Med. Research*, 1903, iv, 378.
33. MacCallum: *Bull. Johns Hopkins Hosp.*, 1907.
34. Duval, C. W., and Howard, C. P.: *Chronic Aleukemic Enlargement of the Lymphatic Glands*, *THE ARCHIVES INT. MED.*, 1910, v, 6.

histological pictures simulating Hodgkin's disease but separable by critical examination and it seems conceivable that such confusion may have arisen in the cases which appeared to confirm the findings of Sternberg.

CASE 1.—*Patient*.—E. W., a female colored child, 3½ years of age, who was admitted to the Philadelphia General Hospital in the spring of 1909. The history was practically negative and the clinical diagnosis was pulmonary tuberculosis, tuberculous meningitis, gonorrheal vaginitis, and the statement is made that the cervical lymph-nodes were slightly enlarged.

#### AUTOPSY

The autopsy showed nothing in addition except that the pupils were unequal, the right being the larger, and there was a deeply excavated bed-sore over the sacrum. The gross anatomical findings were: Advanced tuberculous cerebral leptomeningitis and slight internal hydrocephalus. Chronic adhesive pleurisy; conglomerate caseous, acute miliary and diffuse peribronchial tuberculosis of the lungs with congestion and edema; conglomerate caseous peribronchial lymphadenitis; biliary cysts and miliary tubercles of liver; conglomerate miliary tuberculosis and follicular hyperplasia of spleen; lymphoid hyperplasia of small intestine; cloudy swelling of the kidneys.

#### HISTOLOGICAL EXAMINATION

Histological examination showed cloudy swelling and miliary tubercles of the myocardium; conglomerate peribronchial tuberculosis of lungs with emphysema and slight passive congestion; liver showed perilobular fibrosis, cloudy swelling, passive congestion, miliary and conglomerate tuberculosis; tuberculous biliary cysts of liver; conglomerate tuberculosis and endothelial hyperplasia of spleen; acute parenchymatous nephritis; capsular adenoma and cellular vesiculation of adrenal, and slight chronic interstitial pancreatitis.

A description of a peribronchial lymph-node follows:

Section of lymph-node shows a thick capsule, the deeper layers of which show lymphoid cells, epithelioid cells and typical Langhans giant cells. The greater mass of the section, however, shows nothing but a caseous area. That this is lymph-node is somewhat questionable, inasmuch as none of the true characters of lymph-node are made out; but the capsule, small size, and the circular outline of the tissue indicate to me that this was a completely caseated lymph-node.

A second section of lymph-node, almost certainly peribronchial, shows a normally thin capsule, but with the Mallory connective tissue stain a moderately diffuse connective tissue overgrowth throughout the node. The follicles are of normal size, distinctly outlined, but appear to be less numerous than usual. The presence of a well-marked germinal center of large oval and round cells with rich protoplasm and large vesicular nuclei is noted in many of the follicles. The distinction between cord and sinus in the pulp is entirely lost, there being an irregular intermingling of typical lymphoid cells and proliferated endothelium of the sinuses, these latter cells showing the usual rich protoplasm and large vesicular nucleus. In addition to these cells the section is made peculiar by the presence of a large number of giant cells, the majority of which are like *a* and *b* in the accompanying drawing (Fig. 2). They are large, often reaching 30 microns in a single diameter, usually elliptical, oval or irregular in outline, and have a very finely granular slightly acidophilic protoplasm. The nuclei are multiple, averaging about ten to the cell, are relatively solid, oval, and measure about 3 by 4 microns. Other giant cells like that represented in drawing (*c*) are present, but are much less numerous than the preceding form. These cells are somewhat smaller, but

show a rich protoplasm and contain 2 or 3, rarely more, large, overlapping, vesicular nuclei, sometimes reaching a long diameter of 8 microns. In some of these cells the protoplasm shows slightly coarser granules than in the average. Occasional mononuclear giant cells (*d*), attaining a transverse diameter of 15 microns are encountered and show large, markedly vesicular nuclei such as those seen in the last-mentioned multinuclear giant cell. To draw a sharp dividing line between a cell of this type and the larger endothelial cells is almost impossible. Plasma cells (*e*) are present in small numbers and a few distinctive fibroblasts are found (*f*). Careful search fails to show any eosinophils. The pigment present is small in amount and for the most part is purely anthracotic, showing the variously sized and shaped, absolutely opaque granules characteristic of this material. A few fine brown granules are found, but are inconstant in the various sections. Near the center of the slide a typical miliary tubercle is found, showing a centrally disposed, typical Langhans' giant cell, with surrounding epithelioid and lymphoid cells. In the tubercle and in the adenoid tissue a few bacilli, acid-fast, resistant to ten minutes' decolorization with 10 per cent. nitric acid alcohol, and distinctly beaded, were found.

The entire node is richly vascularized and markedly congested. No hemorrhage.

The diagnosis is acute diffuse tuberculous lymphadenitis of one node, and conglomerate caseous tuberculosis of the other nodes.

Whereas I do not present the case as one of the type described by Delafield and some of his followers, yet in the histological picture there is much that resembles Sternberg's descriptions and drawings. There are several variations from Hodgkin's disease, seen in the node under consideration: first, the presence of a typical Langhans' giant cell and a miliary tubercle; second, the demonstration of tubercle bacilli; third, the very small numbers of giant cells like those described in Hodgkin's disease; and, fourth, the presence in great numbers of giant cells such as are seen at *a* and *b* in the drawing and at *a* in the photomicrograph. The particular feature of these cells to which I direct attention is the rich chromatin content of the nuclei, giving the latter an almost solid appearance. The giant cells described by Sternberg, Crowder, Ferrari and Comotti, Steinhaus, and Schur, to whose papers reference has been made, correspond in this important detail (intense staining of the nuclei), a feature distinguishing these cells from those of Hodgkin's disease, which have larger, distinctly vesicular nuclei in which nucleoli can be made out with great regularity. These writers also noted well-marked necrosis, typical Langhans' giant cells and, in the vast majority of cases, were able to demonstrate the tubercle bacilli in the nodes either by inoculation or staining.

Although the possibility of a coincidence of tuberculous lymphadenitis and Hodgkin's disease is considerable, the cachexia and weakness of the latter apparently increasing the susceptibility of the individual to the former disease, yet the two conditions seem separable by critical histologic and bacteriologic study.

## III. THE SARCOMATOUS TRANSFORMATION OF HODGKIN'S DISEASE

Billroth believed that the condition which we now refer to as Hodgkin's disease was of malignant nature and called it "malignant lymphoma." This nomenclature has been adhered to by many of the German writers, notably Fischer. Ribbert<sup>35</sup> also groups the condition with the malignant tumor formations of the lymphatic apparatus. More recently Gibbons<sup>36</sup> takes the same view.

Other writers feel that a name indicative of the presence of inflammation coincidently with the malignant character is more descriptive, Dietrich<sup>37</sup> suggesting "granuloma-like sarcoma," Benda<sup>38</sup> suggesting "malignant granuloma of the lymphatic apparatus."

A much larger number of contributors to the more recent literature of this subject look on Hodgkin's disease as a distinct malady, well separated from both tuberculosis and malignant disease of the nodes, and I need only mention the names of Clarke, Reed, Longcope, Warnecke, Ronzoni,<sup>39</sup> Duval and Howard, and MacCallum, to show that the weight of authority is with this latter view. My own study leads me to accept this view.

In 1901 Yamasaki,<sup>40</sup> working in Chiari's laboratory, presented a study of five cases which led him to accept Hodgkin's disease as a distinct malady, but added to this series two additional cases, which he thought showed transformation of the original inflammatory mass into a sarcomatous type of tissue.

The first case that he reported was that of a married woman, aged 32, whose blood-examination showed 4,100,000 erythrocytes, 21,000 to 24,000 leucocytes, of which the polymorphonuclears formed 93.5 per cent., lymphocytes, 5.1 per cent., the polymorphonuclear eosinophils 0.3 per cent., and the transitionals 1.1 per cent. The absolute hemoglobin percentage was from 6.72 to 7.12. The patient died after about one year's illness and the autopsy resulted in the anatomical diagnosis of mediastinal sarcoma (thymus) involving sternum, right pleura, left pleura and pericardium and penetrating the left innominate vein. The tumor also involved the lymph nodes of the neck, axilla and region of the stomach. Histologically the tumor and lymph-nodes showed rich lymphoid cell masses, obliteration of follicles, and sinuses, overgrowth of connective tissue, polynuclear giant cells with well-stained irregularly

35. Ribbert: *Geschwulstlehre für Aerzte und Studierende*, Bonn, 1904.

36. Gibbons: *Am. Jour. Med. Sc.*, 1906, cxxxii, 692.

37. Dietrich: *Deutsch. med. Wchnschr.*, 1908, xxxiv, 1188.

38. Benda: *Verhandl. d. deutsch. path. Gesellsch.*, 1901, vi, 123.

39. Ronzoni: *Folia hematologica*, 1909, vii, 160 (abstr.).

40. Yamasaki: *Ztschr. f. Heilk.*, 1904, xxx, 269.

disposed nuclei. In all tissues a distinct infiltrative character was observed. There were no tubercle bacilli.

Yamasaki's second case was that of a married woman, aged 48, presenting the clinical picture of a lymphosarcoma of the neck which ran its course in about one year and terminated fatally. The gross anatomical diagnosis made at autopsy showed sarcoma of the lymph-nodes of the neck involving also spleen, liver, adrenals and mesenteric and peritoneal lymph-nodes. Histologically there was found Hodgkin's disease of the lymph-nodes and spleen, which in the liver shows distinct infiltration of the hepatic parenchyma.

Yamasaki believes that the very rich cellular character of these masses and their distinct infiltration and lack of limitation justify him in concluding that these primarily were cases of Hodgkin's disease which became transformed into a polymorphous-cell sarcoma.

The case which I wish to present in this connection follows:

CASE 5.—*Patient*.—E. E., white, female, 72 years of age; was admitted to the service of Dr. Joseph Sailer, in the Philadelphia General Hospital, Sept. 2, 1908, complaining of nausea and "pain all over." Dr. Sailer has kindly consented to my using this case.

*Family History*.—Father died of unknown cause; mother of typhoid-pneumonia; one brother died of dropsy and one sister died in labor.

*Personal History*.—Widow, whose husband died of typhoid-pneumonia; had two children both of whom died, one at six years of age, the other at three years of age, both of heavy colds. She has used tea and coffee moderately and absolutely denies alcoholism and venereal disease. She has had all the ordinary diseases of childhood but since that period says she has been well except for heavy colds and rheumatic pains at various times. Six years ago her hip was fractured and she has not recovered from this.

*Present Illness*.—About two weeks ago, while in the Almshouse Department, the patient says that she had to go to bed on account of a severe bilious attack during which she was constipated and nauseated, but did not vomit.

*Examination*.—This shows a poorly nourished old woman with a moderately yellow tinged skin, the yellow of cachexia rather than of jaundice. On the right ankle there is a small ulcer. The eyes react to light and accommodation and the conjunctivæ are yellow. The tongue is slightly coated and protrudes in the median line. The pulse is regular, equal and of poor volume and tension. The vessels of the neck are not prominent and the chest expands readily.

Further physical examination of the chest shows no impairment of resonance, fremitus and no adventitious sounds. Cardiac dulness extends from the third rib at midsternum to sixth rib in midclavicular line. Heart-sound is regular and the tones are weak. There is found a systolic murmur at the apex transmitted downward to the border of the sternum. Abdomen is not distended. Liver dulness begins at the sixth rib and extends to the costal margin. Liver and gall-bladder are not palpable. Spleen is not demonstrably enlarged. There are no areas of tenderness in the abdomen. Prolapse of the uterus is noted but no other physical signs.

Urine, on the first examination, was reddish yellow, acid, specific gravity, 1015, and a small amount of sediment. A trace of albumin was present, a few

epithelial casts, granular casts, red blood corpuscles and epithelial cells. A second examination showed the same characters grossly except that the reaction was alkaline. There was no albumin, no casts; a few epithelial cells and triple phosphate crystals. Special examination for bile was negative. Blood-examination on admission showed 2,640,000 red blood cells and 11,500 leucocytes. Examination of feces for tubercle bacilli negative. The temperature varied between 98 and 100, usually showing slight elevation in the evening. The pulse varied between 85 and 105. Respirations on admission were 20 to the minute but increased until at about the time of death they ranged between 35 and 40.

#### AUTOPSY

The autopsy was performed by me about fifty hours after death. General appearance is that of a moderately well-nourished, adult, white female; almost no rigor mortis and slight livor mortis; right lower extremity shows eversion of the foot and a shortening of about 3 inches; swelling and limitation of motion to a right angle and old scars, probably from sinuses. Skin of entire body is bright yellow in color, more marked about the trunk and face. Pupils equal, conjunctivæ dark.

Abdomen shows a generally smooth and glistening peritoneum. Cavity contains 400 c.c. of clear yellow fluid.

Spleen weighs 300 gm., measures 15 by 10 by 5 cm.; thickened and roughened capsule through which can be seen numerous small yellow nodules; cuts with ease and shows a bulging dark red non-bleeding surface in which the follicles and trabeculae cannot be made out; studding the surface are numerous small firm yellow nodules which in many places show central perforation as by a vessel; these are so numerous as to form approximately one-third of the entire organ. At the hilum is found a large nodule similar in nature which apparently surrounds the splenic vein.

Kidneys show chronic interstitial nephritis.

Adrenals grossly are normal.

Bladder is distended with cloudy yellow urine; wall shows marked ribbing; at the point of entrance of the left ureter there is found a hard, dark brown, mulberry-shaped, partially encysted calculus.

Genitalia are grossly normal.

Liver weighs 1760 gm.; measures 28 by 19 by 7 cm.; shows a smooth, glistening transparent capsule; underlying the capsule are found numerous nodules and striae of firm, grayish yellow, tumor masses. Organ cuts with distinctly increased resistance and shows a soft, bulging, slightly bleeding cut surface in which the minute structures cannot be made out because of the diffuse overgrowth of tumor masses. These masses are irregular in size and in the larger areas are seen to lie immediately about the bile ducts. The cut surface is grayish yellow, firm and retracted. Hepatic duct shows a markedly thickened wall without distinct roughening of the mucosa; as it emerges from the liver it is cystic, probably from pressure of enlarged glands on common or hepatic duct. Gall-bladder is markedly enlarged, being 12 cm. in length; wall thin, mucosa thin; it contains a large amount of yellowish gray, slightly viscid, slightly cloudy fluid.

Pancreas is normal.

Stomach is slightly distended with a small amount of yellowish, cloudy fluid; entire wall is somewhat thinned; mucosa is thin and covered with a layer of viscid, dirty mucus.

Intestines: Duodenum and jejunum are slightly congested; ileum shows moderate pigmentation of Peyer's patches and some of the solitary follicles. Large intestines show well-marked pigmentation of the submucosa of the cecum. Appendix normal.

Retroperitoneal lymph-nodes are markedly enlarged and generally adherent, but not confluent, the mass of nodes occupying a position just above the pancreas over the spinal column extending to the hilus of the liver, involving the hepatic duct and compressing the cystic duct, extending downward and growing into the pancreas, apparently pushing aside the pancreatic tissue rather than replacing it. Splenic vessels and portal vein and hepatic artery pass through this mass. Single glands about the hilus of the liver show the same type of enlargement; these glands are firm, yellow, cut with increased resistance, show a moist, bulging cut surface whose finer structures show islands of light gray enmeshed in a network of deeper grayish yellow.

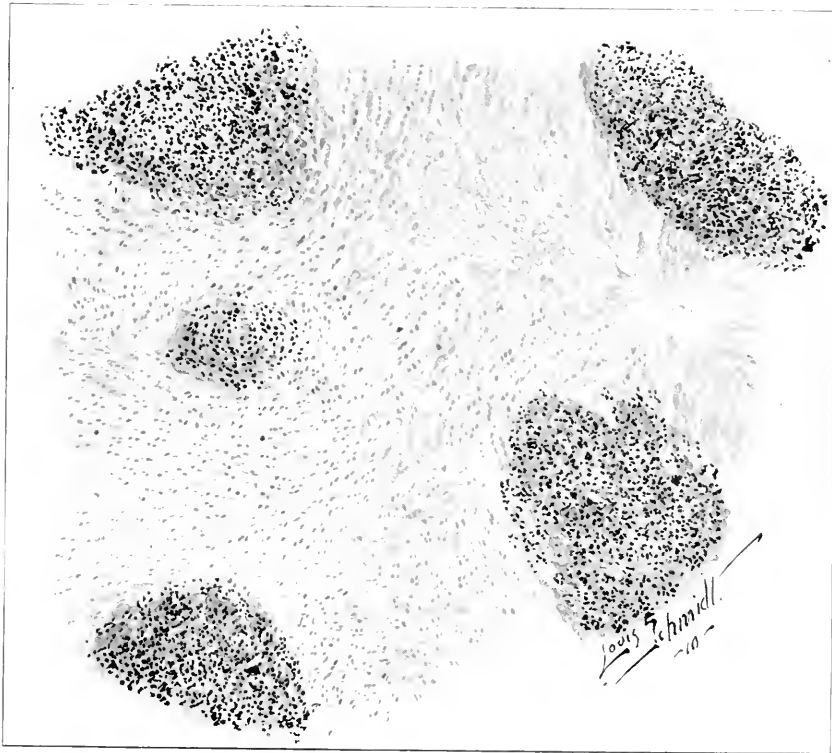


Fig. 3.—Low-power drawing from the liver in Case 5, showing the invasive character of the cell mass.

Lungs show congestion and edema.

The peribronchial nodes are moderately enlarged and soft, cut easily, and show a soft, moist, mottled gray and black cut surface.

Pleurae are normal.

Heart shows moderate cloudy swelling of muscle.

Microscopical examination showed a chronic interstitial myocarditis with fatty degeneration and autogenous pigmentation of the muscle. There was chronic passive congestion of the lung and a chronic interstitial nephritis. The pancreas

showed marked post-mortem degeneration, slight hemorrhage and a well-defined chronic interstitial inflammation. The colon showed a chronic atrophic inflammation and anthracotic pigmentation.

#### HISTOLOGICAL EXAMINATION OF THE LYMPH-NODES

Nodes taken from the retroperitoneal region show marked thickening of the capsule due to fibrous tissue overgrowth and a diffuse reticular overgrowth throughout the node. The follicles and sinuses are completely obliterated by the effusion of the growth. Cellular study of the node shows numerous lymphocytes of the usual type, endothelial hyperplasia, many spindle-shaped cells of connective tissue and a moderate number of plasma cells with rich protoplasm and eccentrically placed solid or vesicular nuclei, and a very small number of eosinophils. Numerous giant cells are present of the type described by Reed, Longcope and others. Mononuclear cells considerably larger than the endothelial cells, showing rich protoplasm and large, markedly vesicular, centrally placed, sometimes indented, sometimes circular, nuclei are present in moderate numbers and, in addition, polynuclear cells showing much the same size with centrally placed, overlapping, oval, distinctly vesicular nuclei, can be seen.

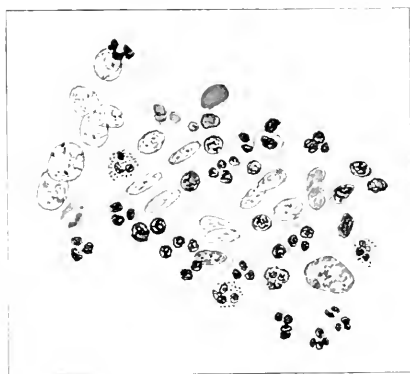


Fig. 4.—High-power drawing from the liver in Case 5, showing the richly cellular character, the lack of reticulum, and the various types of cells described in the notes.

A section from one of the peribronchial nodes shows moderate anthracosis distributed in the usual fashion. There is obliteration of the follicles and sinuses and a cell study shows much the same features as those seen in the mesenteric nodes, except that the fibrosis in the peribronchial lymph-nodes is very much less marked than that in the mesenteries. Examination of these nodes for tubercle bacilli was negative.

Spleen shows moderate thickening of the capsule and trabeculae. The follicles for the most part are obliterated, but, where visible are very small in size and show slight thickening of the central arteries. The splenic pulp shows a diffuse, fine fibrillar, fibrous tissue overgrowth supporting lymphocytes, many endothelial cells, and a few mononuclear and polynuclear giant cells, such as are seen in the lymph nodes. Here and there throughout the section are numerous necrotic areas showing marked karyorrhexis and loss of cellular outline. In no situation can a definite cellular arrangement surrounding the necrosis be made out, but the histologic picture is distinctly not that of tuberculosis. Detailed examination for



tubercle bacilli is negative. A moderate number of fine, golden-brown pigment granules is seen.

Liver: The capsule of Glisson is markedly thickened by the presence of a mass of tissue closely simulating that in the mesenteric lymph-nodes, in which, according to the gross notes, it appears to extend into the liver from the nodes at its hilus. This tissue shows an exceedingly rich cellular arrangement of fibroblasts, endothelial cells and a few mononuclear and polymorphonuclear eosinophils, plasma cells, and relatively small mononuclear and polynuclear giant cells. This tissue is peculiar in that it is very much more cellular than that seen in the mesenteric nodes, and apparently represents a much more rapidly proliferating mass. The growth does not confine itself to the capsule of Glisson, but can be seen to penetrate clearly within the liver lobules, partly pushing aside the liver cells and partly substituting itself for these cells (Figs. 3 and 4). The protoplasm of the essential hepatic cells shows marked cloudy swelling, the cells being poorly outlined, granular, poorly stained. The nuclei are more or less obscured in many cases, show distinct peripheral grouping of the chromatin and in some places well marked fading. The cell chains have been broken up and the lobular arrangement is still vaguely preserved. The central zone of the lobule shows well marked hemosiderin pigmentation of the cells and the presence of many minute vacuoles, evidently of fat. The vein itself is moderately congested. The structures of the capsule of Glisson are lost within the new growth, and it would seem probable that the advanced cellular degeneration depended to a considerable degree on the cutting off of nutrition by the growth within the capsule of Glisson.

The diagnosis would appear to be Hodgkin's disease of considerable duration (third stage of Longcope) of mesenteric lymph-nodes and spleen; more recent Hodgkin's disease of peribronchial lymph-nodes; cloudy swelling and fatty degeneration of liver, with a polymorphous cell sarcomatous invasion.

Somewhat similar invasion of the liver was seen by Reed in Case 1 of her series, that of a boy 9 years of age, the section also showing definite invasion of a vein. Longcope describes the livers of two patients: Patient 1, a man aged 34, and Patient 2, a boy aged 7, in which there was distinct invasion of the liver parenchyma, but without noticeable change in the character of the invading mass from that seen in the lymph-nodes. Gibbons<sup>41</sup> observed the same features in the livers of three of his patients and largely because of this feature, associated with invasion of the capsule of the lymph-nodes, he believes that Hodgkin's disease should be classified with the malignant tumors.

This feature, however, is an unusual one and seems to be very inconstant in the picture, so that it can hardly be looked upon as a necessary accompaniment of the disease. I therefore incline to the view held by Yamasaki that such invasions are to be looked on as showing a malignant transformation of a disease that primarily is of the nature of a chronic inflammation, and to point out, as does Yamasaki, the very rich cellular character of the growth. This rich cellular content, the almost complete lack of reticulum, the young type of most of the nuclei, the evident invasion, with much less compression than I have often seen in many sec-

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41. Gibbons: *Am. Jour. Med. Sc.*, 1906, cxxxii, 692.

ondary cancers of the liver, are evidence of rapid proliferation of a growth which invades the liver, produces degenerations of the liver parenchyma, substitutes itself for the liver tissue and is thus clearly malignant. These features are clearly brought out in the accompanying drawings. I fully appreciate that invasion of tissue occurs in the definitely known infectious granulomata, such as tuberculosis, actinomycosis, syphilis, glanders, leprosy, and the lesions, when invading peripherally, as a rule necrose centrally; but the richness of cells in the invading portion shows no differences from the arrangement of non-invading parts. In Hodgkin's disease, however, the invading masses lose much of their inflammatory character (connective tissue overgrowth), take on a very rich cell character and show little or no tendency to central necrosis. Dietrich<sup>16, 37</sup> thinks that the change in the cell mass itself is insufficient to justify the conclusion, and, if there is no change, the condition should be looked on as sarcoma from the beginning. The transformation of the tissue at the edge of a leg ulcer into carcinoma, or of a gastric ulcer into a carcinoma, is associated with very slight change in the essential character of the cells, the malignant character being evidenced by the invasion of the cells into the deeper tissues, so that there seems to me sufficient reason for thinking that the invasive character of the Hodgkin's disease masses and their greater richness in cells justifies the belief that there is here a transformation of this chronic granulomatous inflammation into a malignant growth, whose cell character is so varied as to warrant the use of the name polymorphous-cell sarcoma. This statement is made with the mental reservation that more precise knowledge as to the essential nature of the disease must be gained before final conclusion as to this point can be drawn.

#### CONCLUSIONS

I feel that sufficient new material has been studied in connection with the previously published reports to justify the following conclusions:

1. Hodgkin's disease is a distinct pathological entity.
2. Hodgkin's disease may produce or be accompanied by high-grade anemia, usually of the secondary type, occasionally of pernicious type.
3. The presence of histo-eosinophilia is not of great diagnostic significance.
4. Surgical removal and competent examination of the involved lymph-nodes may lead to an accurate diagnosis.
5. Although tuberculosis of the lymph-nodes and Hodgkin's disease may occur coincidentally, tuberculosis is not necessarily a related condition. Hyperplastic tuberculous lymphadenitis may present a histological pic-

ture somewhat confusing with that of Hodgkin's disease. The giant cells of this form of tuberculosis differ from those of Hodgkin's, in that the former show relatively solid nuclei, and the latter distinctly vesicular nuclei.

6. Pending the discovery of the essential nature of the disease, it may be said that Hodgkin's disease, a chronic granulomatous inflammatory process, may undergo transformation with assumption of malignant characters.

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# AUSCULTATORY BLOOD-PRESSURE DETERMINATIONS

## A PRELIMINARY REPORT

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In October, 1905, Korotkow, of St. Petersburg, first advocated the determination of blood-pressure by auscultation. His method has been thoroughly studied, especially in Germany, and has been adopted by many observers as a routine procedure. Apparently it has been little, if at all, discussed in American or English literature, and in view of the importance of proving or disproving certain claims which have been made for it, it has seemed advisable to present this preliminary report of a series of observations which have been undertaken, in the hope that others may be induced to gather testimony.

The usual manometer and its equipment are employed in the auscultatory method, and the brachial artery is selected for auscultation at a point from two to four cm. below the cuff. The blood-current is shut off in the usual manner and the first sound which is heard, as, with the fall of the mercury, the blood-current reaches the point selected for auscultation, corresponds to the maximum systolic pressure. Then follow variations in the sounds, which will be discussed at length, and finally, with the release of all pressure in the cuff, the disappearance of all sounds. The last phase, according to Ettinger,<sup>1</sup> corresponds to the minimal or diastolic pressure.

Korotkow explains the first sound through the forcing apart of the vessel walls by the first stream of blood which reaches the artery below the cuff. He maintains that the lower part of the brachial artery, during the time that compression is exerted above it, is in a condition of complete relaxation and that the first blood-stream causes a sudden sharp stretching of the walls with the consequent production of sounds. Bozowski advanced the theory that the first and succeeding sounds originate in the heart and are transmitted by the blood-stream, but, as Krylow observes, this view is entirely negated by the fact that all sounds cease with the release of compression.

Ehret<sup>2</sup> believes that the suddenness of the distention, and not the amplitude of the blood-wave, determines the intensity of the sound. The

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1. Ettinger: *Wien. klin. Wchnschr.*, 1907, xx, 992.

2. Ehret: *München. med. Wchnschr.*, 1909, lvi, 959.

fact that the sounds diminish a short distance below the cuff he ascribes to the less complete emptying of the artery, due, in turn, to peripheral arterial and venous pressure.

The theory that the sudden stretching of the relaxed vessel-wall produces the first sound is in accordance with the well-known physiological fact that independent sounds can originate in a blood-vessel only when the distention of that vessel at the moment of transmission of the blood-wave is at once sudden and of considerable intensity.

That the phenomena of the sounds are largely dependent on the size of the vessel as well as on its accessibility can be proved by the observation that while the cuff is applied to the forearm, the observer hears the sound exceptionally and only for a short time over the radial or ulnar artery. Finally it is evident that the resonating character of the cuff plays a most important rôle, since, with simple compression by an Esmarch bandage, the sounds are not, as a rule, audible.

Of greater interest than the determination of the maximal and minimal pressure is the interpretation of the intermediate sounds. The following sequence can be determined in the average case.

The cycle begins with the passage of the first waves of blood under the cuff. This produces a clear-cut sound resembling the tap of embryocardial rhythm and is known as the "first phase." Succeeding this a murmur becomes audible, more or less clearly defined and of varying duration. In the average case the murmur at first accompanies the sound but soon replaces it. The period of audible murmur is known as the "second phase." At the inception of the next or "third phase" the murmur disappears and is substituted by a clear sound. With the further fall of the mercury this clear sound becomes dull. At times this transformation is clear-cut and easily recognizable—again it occurs more gradually. Ettinger<sup>1</sup> and Fischer,<sup>3</sup> describe this transformation as the "fourth phase." The latter believes that it coincides with the diastolic pressure. Ettinger considers that it precedes true diastole and that the latter coincides with the disappearance of all sounds, which he calls the "fifth phase."

Krylow, in a previous communication, described only the first three phases. My own experience coincides with that of Ettinger and the differentiation into the five phases would seem to be possible in a large majority of cases.

In a discussion of these phases of the auscultatory phenomena it might be well to recall that, according to Landois and Corrigan, the rapidity of a blood-stream in a vessel is indirectly proportionate to the

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3. Fischer: *Ztschr. f. diätet. u. physik. Therap.*, October, 1903, p. 391.

diameter of the lumen of that vessel. As the rapidity of the stream is the chief factor in the production of the sudden stretching of the vessel wall, which, in turn, produces the vibration which we hear as the arterial sound, this physiological fact becomes of much importance in the explanation of the auscultatory phenomena.

Krylow considers that the first sound produced is the loudest and ascribes this to the fact that, the lumen of the vessel under the cuff being at a minimum, the rapidity of the blood-stream is consequently maximal and thereby fulfills the conditions necessary for a sudden stretching of the walls of the vessel below the cuff.

Ettinger claims, however, that the greater volume of blood which passes under the cuff by the time the third stage is reached is capable of producing a more marked vibration of the vessel walls even though the rapidity of the current is less. With the appearance of the fourth phase the vessel walls are approaching a normal degree of expansion and vibration is consequently less marked. Added to this factor are the slowing of the blood-stream and the collapse of the cuff whereby it loses its resonating qualities. Ettinger found that in 90 per cent. of his 235 cases studied in Janowsky's clinic, the third phase was distinctly louder than the first. Fischer, from his study of 180 cases, is in practical accord with this opinion. The origin of the murmur during the second phase would seem to be due to the formation of whirls in the blood-stream, caused by the blood rushing from the obstruction at the cuff into the area of increased diameter below it. Friederich, in differentiating between murmurs and sounds, believed that the former depend on vibrations (*Schwingungen*) in the blood-stream, the latter on vibrations of the vessel walls.

In 1854 Heynsius stated that the essential factor in the production of a murmur was a narrowing of the lumen of the vessel and that rapidity of the current, to which Cheveau ascribed so much importance, alone was unable to produce a murmur. Friederich, believing with Cheveau that the rapidity of the blood-stream is a factor of great importance, considers that the viscosity of the blood, through its effect on the rate of flow, likewise influences the production of murmurs. The loud and prolonged murmur which Fischer heard over the brachial artery in certain anemic patients would seem to corroborate Friederich's view. This prolongation of the murmur (second phase) occurred at the expense of the third phase. At times, also, the first phase was lacking and the fourth phase was longer than normal. These phenomena occurred with a low diastolic pressure.

In cases of high diastolic pressure, on the other hand, Fischer found that the first phase was always loud and clear and the second phase, when present, was short but clear. If the third phase were short, the fourth phase could not be heard.

In arteriosclerosis, with hardening and loss of elasticity of the vessel walls, the auscultatory phenomena, according to Krylow, are apt to be more pronounced, since the back-pressure at the cuff probably causes some dilatation of the vessel above it, while the lumen of the vessel is smaller than normal. Both of these factors cause an increased rapidity in the transmission of the blood-wave when pressure in the cuff is released, which in turn favors the vibration of the vessel-walls.

In high-grade thickening of the arterial walls, however, especially where calcification had occurred, Fischer found that the sounds were distinctly less loud than normal, the more so in the arm which showed the greater degree of hardening. According to Ettinger's experience the rapidity of the flow distinctly increases the auscultatory phenomena. This accords with the belief that these sounds are dependent on vibration in the vessel-walls.

Since Janowsky has demonstrated an increased pulse celerity in 60 per cent. of all cases of arteriosclerosis, Ettinger considers that we should be on guard against a possible hypertonia when we find in young individuals that the auscultatory sounds are very clear. This, however, needs confirmation. The factors which are to be considered, therefore, in the interpretation of the varying sounds, are:

1. The degree of narrowing of the vessel.
2. The elasticity of the vessel.
3. The size of the pulse-wave.
4. The rapidity of its transmission.

The first two in clinical practice, can only be gauged by the presence or absence of sclerotic thickening. The size of the pulse-wave can be inferred from the feel of the artery while the rapidity may be judged in part by the number of beats. Fischer believes that the character of the sounds heard over the vessels corresponds in general to the sounds which are heard over the heart. He considers that the third phase is the most important, and that from its characteristics we can surmise the degree of heart vigor (*Gröss der Herzarbeit*).

In two of Fischer's cases of weakness of the third phase, in which the efficiency of the heart was apparently unimpaired, the possibility of stenosis of the aortic orifice was considered. An autopsy, in one of these cases, proved the correctness of this assumption. In general he found that the intensity of the third phase corresponded to the height

of the blood-pressure. In several exceptions to this rule—cases of nephritis with high pressure—beginning failure of the heart could be demonstrated.

The duration of the third phase Fischer also considers of great importance. In high pressure with loud sounds, the third phase was always prolonged. In one case of weak heart, the duration was short but became longer with improvement in the condition of the heart. In some cases of very high pressure, he heard a lighter, clear sound between the second and third phases.

Fischer also heard Traube's change of pulse in some cases, the sounds diminishing during inspiration, especially if it were deep, becoming more clear during expiration. I have observed this in several instances but am unable to indicate its significance.

From Krylow's experience, atypical auscultatory phenomena point to different degrees of insufficiency of the heart muscle: for example, in the absence of a murmur, to relative insufficiency; in the absence of sounds and the presence of a murmur, to well-marked weakness of the heart (*vollständig Schwach*). In these cases the amount of blood and the rapidity of the blood-stream are not sufficient to produce the sound.

As has been said, Ettinger finds that the second sound is louder than the first in 90 per cent. of his cases. In the remaining 10 per cent. the weakness of the second sound he considers to be of pathologic significance. His specific findings are as follows: In twenty-eight cases of cardiac insufficiency with dyspnea and edema, the third phase was absent nine times. Since this phase depends on a moderately large pulse-wave and moderate rapidity in its transmission, which in turn, depend upon a strong systole, the absence of these would point to heart-weakness.

In two other cases the second and fourth phases were absent and in four cases the second phase was lacking. These were all cases of high-grade heart-weakness. Ettinger believes that absence of the third phase alone denotes moderate weakness of the heart muscle while coincident absence of the second and fourth phases indicates that the weakness has reached a high degree. In two of his cases, when there was improvement of the heart, there was a return of the third phase and in two others, with increase of the weakness, there followed a disappearance of the second and third phases. In a case of fatal pneumonia, with sudden cardiac failure, on the day of death there occurred a sudden disappearance of the second and third phases. He emphasizes these facts, namely, that in severe disturbances of compensation certain auscultatory phases vanish, while in severe anemias, where the blood flows more rapidly than normal, the auscultatory sounds, according to his experience, have been



very clear. He suggests that in polycythemia with splenomegaly the reverse would probably be found.

Authorities are not in accord as to the exact determination of diastole by the auscultatory method. Some believe that the fourth phase, at the moment when the clear sound becomes dull, represents the true diastole. With Ettinger I am inclined to accept the fifth phase (disappearance of sounds) as the indication of diastole. On account of its length, the discussion of the subject may properly be left for a future article.

The practical application of the auscultatory test by the single operator is at least as easy as with any other method, provided certain conditions obtain. First and most important is the complete cooperation of the patient. Any movement of the arm, or body, even the slightest, may produce a sound which can easily be misinterpreted. Second, for the average operator, confusion is easily introduced by extraneous noises. Third, the cuff must fit perfectly. In an emaciated patient this perfection, especially with the Janeway cuff, is, at times, difficult to secure. Finally, in many cases of aortic regurgitation, the determination of diastolic pressure by auscultation is, obviously, impossible, owing to the presence of the well-known "pistol-shot" sound.

Against these objections can be set the greater accuracy afforded by auscultation and, especially, the more satisfactory determination of the diastolic pressure. Most of us, I am sure, have often been dissatisfied with our interpretation of mercurial oscillation, and although many are proficient in the determination from the pulse alone, this can hardly be considered as accurate as the auscultatory test.

In my examinations by the auscultatory method, I have followed, in the main, the recommendations of Ettinger, calculating diastole as the fifth phase. All the observations have been made on patients in the medical wards of the Presbyterian Hospital in the service of Dr. Joseph Sailer, to whom I wish to express my indebtedness.

The Stanton sphygmomanometer with the Janeway 14-cm. cuff was employed. At a point from 2 to 5 cm. below the cuff, the brachial artery was auscultated with a double stethoscope. The mean of two or more observations was taken in almost every instance. An assistant took the manometer readings, in order to obviate the factor of personal equation. Sterzing<sup>4</sup> employs a 6-cm. cuff, claiming somewhat lower figures than those obtained with the broad cuff. The same author insists on the patient resting in bed for a half an hour before the tests, which should be made at the same hour each day in any comparative series of examinations.

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4. Deutsch. med. Wchnschr., 1909, xxxv, 1874.

Fischer insists on the importance of allowing complete collapse of the cuff between observations in order to obviate congestion which might, in the presence of a weak heart, depress the systolic reading and cause the third phase to lose some of its force. The same author also rejects the readings in the first observations on nervous individuals, as the psychic disturbances must be discounted. Several improvements in recording my cases were made as the study advanced, so that some of the first results were not used, owing to a lack of sufficient data in reference to the variations in the different phases. The final scheme included the following:

Name.  
Age.  
Diagnosis.  
Pulse-rate.  
Size and rhythm.  
Sclerosis.  
Size of arm.  
Examination of heart.  
Signs of failing compensation.  
Systolic and diastolic pressure, according to the method of Strasburg.  
Auscultatory phases.  
Notes on auscultatory phenomena.

From the examination of sixty-three cases, which form the basis for this preliminary report, the following results may be tabulated:

In sixty-one cases, the auscultatory MX averaged 16.7 mm. higher than that determined by palpation.

In two cases, the reverse occurred, the palpatory MX being higher than the auscultatory. In one case the difference was only 2 mm., and in the other, 27 mm. In the latter, however, the arm was excessively thin, and all the auscultatory phenomena were difficult to determine.

In forty-one cases, diastole, as determined by auscultation, averaged 15.5 mm. lower than that determined by the visual method.

In five cases, diastole by auscultation averaged 7.7 mm. higher than that by the visual method.

In two cases the results were equal.

In one case, diastole could not be determined by auscultation.

In eleven cases, diastole could not be determined by inspection.

The maximum pressure being higher by the auscultatory method and the minimum being lower, it follows that the pulse-pressure is greater in the auscultatory than in the visual method. Ettinger found an average difference of 13.2 mm., while my results give a higher figure, 24 mm. Finally, there remain to be considered the variations from the normal sounds heard during the cycle.

In one case, there was absence of the second and fourth phases. This occurred in a patient of 74 years with myocarditis and nephritis, with enlarged heart, but weak sounds, especially at the base.

In one case there was absence of the third and fourth phases, in a patient with mitral and tricuspid regurgitation, exhibiting marked symptoms of ruptured compensation. In another case of mitral and tricuspid regurgitation, the second, third and fourth phases were absent. In a third case of mitral and tricuspid regurgitation, the third phase was absent. Arteriosclerosis was well marked in this patient. In another instance of absence of the third phase, myocarditis and slight sclerosis were present. In another advanced case of valvular disease, aortic and mitral and tricuspid regurgitation, the second and third phases were absent.

In one case of myocarditis and marked sclerosis there was an absence of the fourth phase. [In one case of myocarditis with slight edema but little sclerosis there was the absence of the murmur.] In one case of general tuberculosis, two days before death, with profound asthenia, the second, third and fourth phases were almost indistinguishable. In two cases, the murmur persisted throughout the cycle. One was a case of carcinoma of the stomach; the other, of neurasthenia.

In all three of these cases, however, the patients being women, the arm was so thin as to prevent accurate fitting of the cuff. In one case of chronic asthma, during a severe exacerbation, the second, third and fourth phases were difficult to distinguish, but the excessive respiratory disturbance in the presence of a low pressure (111 mm.) was the evident cause.

In the following cases, no difficulty was experienced in determining all of the phases.

Arteriosclerosis with systolic aortic murmur.

Mitral regurgitation with marked arrhythmia and slight sclerosis with no signs of lost compensation.

Chronic endocarditis with acute rheumatism and pericarditis and good compensation.

Finally in one case of aortic regurgitation, the fifth phase could not be determined. In the remaining cases the auscultatory phases showed no change from normal and the cardiovascular symptoms were unimportant. On the basis of this small number of cases, definite conclusions are, of course, unwarranted.

The results of my observations agree, in the main, so closely with the published reports that it seems desirable to embody them, in their unfinished state, in a preliminary communication. That practical con-

clusions of real value as to the efficiency of the cardiovascular system may be reached through the medium of Korotkow's method seems to be a justifiable hope.

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## SPECIFICITY OF THE NOGUCHI MODIFICATION OF THE WASSERMANN REACTION\*

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Early in 1909 Noguchi<sup>1</sup> brought to the attention of the medical profession a modification of the Wassermann system of complement fixation test for syphilis. It was in reality a new system for the detection of the so-called syphilitic antibodies, based on the Bordet-Gengou<sup>2</sup> phenomenon of complement fixation, as in the Wassermann method, but using an anti-human hemolytic system as indicator instead of the antish sheep system of the original method. Although differing from the latter in technical application, this variation in the hemolytic indicator represents the fundamental difference between the two systems.

Noguchi claimed for his method simplicity, greater facility of application, greater sensitiveness in the detection of the specific reacting bodies, and the possibility of so preparing the various reagents used in the test as to make it available for every laboratory worker or physician familiar with clinical laboratory methods.

A glance at Noguchi's original protocol will make it apparent that the antihuman system has the advantage over the Wassermann system in simplicity and ease of application. The small amount of the patient's blood necessary, the ease with which normal human corpuscles can be procured as compared with the difficulty often encountered in obtaining fresh sheep's blood, and the availability of hemolytic amboceptor and antigen-extract dried on filter-paper successfully support these claims.

It can scarcely be doubted that the antihuman method is a more delicate one for the detection of syphilis, active or latent, than the antish sheep system of Wassermann.<sup>3</sup> A review of the results of many investigators<sup>4</sup> in this country who have carried out the two methods side by side in more than 2,800 cases of syphilis shows that in practically every stage of the disease the newer system gives a larger percentage of positive results (Table 1). My own comparison of nearly two hundred cases of

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\* From the Pathological Laboratory of the Mount Sinai Hospital.

1. Noguchi, H.: *Jour. Exper. Med.*, 1909, xl, 84; *München. Med. Wehnschr.*, 1909, lvi, 494.

2. Bordet and Gengou: *Ann. de l'Inst. Pasteur.*, 1909, xv, 289.

3. Wassermann: *Deutsch. med. Wehnschr.*, 1906, xxxii, 745.

4. Noguchi: *Internal. Clin.*, 1910, Series 20, i, 23.

TABLE 1.—COMPARISON OF WASSERMANN AND NOGUCHI METHODS IN CASES OF SYPHILIS

—Primary Syphilis—				—Secondary Syphilis—				—Tertiary Syphilis—				—Latent Syphilis—				—Congenital Syphilis—				Cerebrospinal Syphilis.			
No. of Cases.		W.	N.	No. of Cases.		W.	N.	No. of Cases.		W.	N.	No. of Cases.		W.	N.	No. of Cases.		W.	N.	Total.			
Noguchi .....	23	73.9	86.9	79	83.7	96.2	65	80.0	87.6	59	61.6	75.5	4	100.0	100.0	5	....	....	80.0	235			
Fox .....	7	100.0	100.0	37	97.0	100.0	32	71.0	81.0	54	46.0	62.0	1	100.0	100.0	..	....	....	....	131			
Kaplan .....	138	90.0	97.0	281	86.0	98.0	191	73.0	81.0	79	51.0	75.0	20	90.0	90.0	..	....	....	....	709			
Swift .....	16	81.0	81.0	76	92.0	97.0	45	80.0	88.0	85	55.0	62.0	4	100.0	100.0	..	....	....	....	226			
Cosson-White ..	14	86.0	100.0	146	98.0	99.0	47	80.0	80.0	28	60.0	64.0	39	100.0	100.0	35	80.0	80.0	80.0	309			
Kaliskel .....	10	100.0	100.0	50‡	94.0	100.0	75§	60.0	80.0	...	....	....	11	100.0	100.0	15	66.0	80.0	80.0	161			
Total .....	208	88.0	94.0	639	92.0	98.0	455	74.0	83.0	305	54.0	68.0	79	98.0	98.0	55	73.0	80.0	80.0	1771			
Noguchi .....	70	....	92.8	197	....	96.0	177	....	88.9	270	....	74.4	17	....	100.0	..	....	....	....	731			
Craig .....	37	....	51.0*	50	....	78.0	16	....	68.7	12	....	83.3	4	....	75.0	..	....	....	....	119			
Potter (Afr.)...	7	....	86.0	71	....	98.6	46	....	78.0	58	....	66.0	...	....	....	..	....	....	....	182			
Great .....	9	....	100.0	24	....	89.0	5	....	60.0	9	....	11.0†	2	....	100.0	1	....	100.0	50				
Berghausen .....	...	....	....	15	....	93.0	9	....	88.0	6	....	66.0	4	....	75.0	..	....	....	....	34			
Total .....	123	....	82.0	357	....	91.0	253	....	73.0	355	....	62.0	27	....	87.5	..	....	100.0	1116				
Grand total ..	331	88.0	93.0	1026	92.0	95.0	708	74.0	80.0	660	54.0	63.0	106	98.0	94.0	55	73.0	85.0	85.0	2887			

\* Includes very early cases.

† Majorly under treatment.

‡ Untreated.

§ Includes latent cases.

syphilis by the two methods substantiates the above findings. In primary, secondary, and tertiary cases that have not had treatment the differences are not strikingly great. It is in the cases of late latent syphilis and in the so-called metasymphilitic conditions that I have found the antihuman system a more delicate index of the presence of the virus of syphilis in the blood, as evidenced by a positive reaction.

At this point I shall point out the chief reason for the difference in the outcome of the test on the same serums examined by the two systems under discussion. It is a well-known fact that certain serums contain natural hemolytic agents for foreign corpuscles. Human serum in particular frequently contains such an hemolytic amboceptor for sheep's corpuscles, used as hemolytic indicator in the Wassermann system. Aschenheim<sup>5</sup> found that the blood of an eight-day-old child already possessed this property. As a rule, its presence is rather inconstant before the second year of life, increasing from this time up to puberty. My own experience gained by an analysis of the antisheep amboceptor content of the blood in over two hundred cases, normal and syphilitic, shows that this substance is present in about 53 per cent. of the serums in quantity varying from a fraction of the amount, to ten or more times the amount necessary to hemolyze completely the bulk of corpuscles used in the test, 1 c.c. of a 5 per cent. emulsion of sheep's cells. Now, keeping in mind the quantitative relationship existing between complement and amboceptor, as pointed out by Morgenroth and H. Sachs,<sup>6</sup> it is quite certain that in a case of syphilis or metasymphilis in which complement is not completely fixed in the test, the presence of this excess of natural hemolytic amboceptor plus the two units of artificial amboceptor required in the original protocol would so activate the remaining free complement as to cause any degree of hemolysis, from partial to complete. Thus, a negative reaction with the Wassermann method might easily be the reverse with the Noguchi method. The above fact is so well established in immunity work that its bearing on the detection of the reacting bodies cannot fail to be of significance. In a small percentage of cases of syphilis, usually many years after infection, more frequently in metasymphilitic conditions, and most commonly in syphilitics undergoing mercurial treatment or not long after it, the Wassermann test will result negatively, the Noguchi positively on account of the above phenomenon. In Table 2 I have recorded some examples illustrating this fact.

5. Aschenheim: *Centralbl. f. Bakteriol.*, 1909, xlix, Abt. 1, Orig. p. 124.

6. Ehrlich: *Arbeiten zur Immunitätsforschung*, Berl. klin. Wchnschr., 1902, No. xxv, 359.

TABLE 2.—NOGUCHI METHOD POSITIVE, WASSERMANN NEGATIVE

	N.	W.	
Congenital syphilis .....	+	—	Under Hg treatment till recently.
Secondary syphilis .....	«+	—	Under Hg treatment till 3 months ago.
Secondary syphilis .....	+	«+	Under Hg treatment.
Latent syphilis .....	«+	—	Chancre many years ago.
Tertiary syphilis ..	«+	—	
Tertiary syphilis .....	+	«+	Excess natural antisheep amboceptor.
Tertiary syphilis .....	+	—	Gumma pyloric end stomach.
Tertiary syphilis .....	«+	—	Under Hg treatment.
Latent syphilis .....	«+	—	Chronic intermittent treatment 7 years.
Cerebrospinal syphilis .....	+	—	
Cerebrospinal syphilis .....	+	(±)	Wassermann almost negative.
Cerebrospinal syphilis .....	+	(±)	Wassermann only suspicious.
Aphasia .....	+	—	
Tabes .....	+	—	Great excess antisheep amboceptor.
Tabes .....	+	«+	Bauer test, 3 units natural amboceptor.
Periostitis, specific .....	+	—	Bauer test, 2 units natural amboceptor.
Stricture rectum .....	+	—	Bauer test, natural amboceptor.
Epiphysitis, specific .....	«+	—	
Endometritis (abortions) .....	+	(±)	Wassermann suspicious.
Osteomyelitis, specific .....	+	«+	No natural amboceptor; goes negative on addition of two units artificial amboceptor.
Chronic endocarditis, nephritis..	«+	—	Bauer test suspicious; 4 units natural amboceptor present.
Diabetes insipidus .....	«+	—	Bauer test positive; excess amboceptor.
Hodgkin's disease .....	+	—	Chancre about 20 years ago.
Proctitis .....	«+	—	Under Hg treatment till recently.
Ulcus cruris .....	+	—	Chancre 25-30 years ago.
Spastic paraplegia .....	«+	—	Spinal fluid negative.

+, Positive. —, Negative. «+, Weakly positive to moderate. (±), Only suspicious.

The use of active serum is another factor influencing the outcome of the reaction. Heating human serum as required in the original method of Wassermann has the effect of reducing the antibody content materially, even to one-fifth of the original content. This fact, pointed out and emphasized by Noguchi, was the reason for the use of active serum in his system. In the systems of Hecht and M. Stern active human serum in comparatively large dose is used.

Hans Sachs<sup>7</sup> has shown that the use of active serum in the Wassermann system gives a larger percentage of positive reactions, but he

7. Sachs, H.: Verhandl. d. deutsch. dermat. Gesellsch., 1908, x, 167.



proved, as did Boas,<sup>8</sup> that normal active serum occasionally reacted positively also. This makes it apparent that the use of active serum is inadvisable in the old method, as will be mentioned in more detail below. In the Noguchi method, however, the amount of active serum used, 0.02 c.c., is not sufficient to cause non-specific fixation. My comparative analysis of over 700 cases, using active serum in the Noguchi method and serum heated to 56 C. for thirty minutes in the Wassermann method, proves this conclusively (Table 3).

The argument has been raised that the presence of isohemolysin in human serum might prove a disturbing factor in the antihuman system. I have examined a fairly large number of cases of cancer and tuberculosis, in which isohemolysis occurs most frequently, and with the quantity of serum used in the test I have encountered this phenomenon so infrequently as to render it a negligible factor.† In the few cases in which hemolysis occurred before the addition of hemolytic amboceptor, if the control tubes with the same corpuscles were not affected, the patient was found to have a carcinoma. In cases of syphilis, under the same conditions, I have never encountered this phenomenon. A slight alteration in the technic so as to cause incubation for fixation of complement before the addition of the human corpuscle suspension, and the use of the patient's own corpuscles in these cases as recommended by Noguchi, will altogether obviate this difficulty.

Thus it seems to be the consensus of opinion, and my own work in this field tends to confirm it, that the antihuman system of Noguchi is somewhat more sensitive than the original Wassermann test in the detection of syphilis, chiefly owing to the above-mentioned characteristics of human serum.

Now as to the preparation of the chief reagents used in the test on filter-paper so as to make the serum diagnosis of syphilis a more generally applicable test: I may mention here that the worker in a well-equipped laboratory with a moderate degree of training in immunity work will not find it necessary to rely on material so prepared, although he often will find the paper reagents of great convenience. In the larger laboratory the Noguchi system can be carried out with liquid reagents prepared and titrated just as in the regular Wassermann method. Noguchi himself originally used them so, reserving the use of the reagents on paper for those unable to prepare the material themselves, for distribution, and for emergencies.

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8. Boas: *Berl. klin. Wehnschr.*, 1909, xlvii, 400.

† Isohemolytic serum is seldom active in a greater dilution than 1 to 10.

TABLE 3.—ROUTINE CASES FROM THE WARDS FOR DIAGNOSIS. WASSERMANN AND NOGUCHI SYSTEMS APPLIED \*

	Neg	Pos.	
Anemias—splenic pernicious, secondary..	8	0	
Chronic endocarditis .....	26	0	
Chronic endocarditis and nephritis.....	5	1	
Nephritis, acute and chronic.....	21	1	Chancre three years ago.
Myocarditis .....	5	1	Autopsy.
Hodgkin's disease .....	8	1	Chancre twenty years ago.
Leukemias .....	4	0	
Banti's disease .....	4	0	
Aortic regurgitation, aortitis.....	3	1	
Aortic stenosis .....	2	0	
Aneurism .....	2	1	
Arteriosclerosis .....	6	2	
Paroxysmal tachycardia .....	1	0	Perforated septum, tertiary.
Arteriosclerosis .....	6	2	
Heart-block .....	1	0	
Cirrhosis liver .....	4	6	
Chronic cholecystitis .....	3	0	
Cholelithiasis .....	4	0	
Acute yellow atrophy.....	1	0	
Arthritis deformans .....	8	5	One case positive with Wassermann.
Arthritic conditions—chronic, infectious, Still's metabolic, etc.....	25	0	Some inhibition with the Noguchi with active serum.
Auto-intoxication, Brill's disease, etc...	5	0	
Typhoid .....	4	1	Chancre twenty-eight months ago
Dysentery .....	1	0	
Gastric conditions—gastralgia, hyperacid- ity, gastritis, ulcer.....	6	1	Gumma pylorus at operation. See Table 2.
Pulmonary conditions — pneumonia, ab- scess, asthma, emphysema, pleurisies, tumor .....	15	0	
Pulmonary tuberculosis .....	8	0	
Diabetes mellitus .....	3	0	
Diabetes insipidus .....	2	1	Wassermann negative; Bauer and Noguchi tests positive.
Asthenia .....	1	0	
Achondroplasia .....	1	0	
Hydrocephalus .....	3	0	
Rickets .....	1	0	
Marasmus .....	1	0	
Craniotabes .....	10	0	
Varicella .....	1	0	Faint inhibition with Noguchi.
Plumbism .....	1	0	
Myxedema .....	1	0	
Gout .....	1	0	
Trichinosis .....	2	0	
	208	22	

\* The results are identical with both systems unless otherwise indicated.

TABLE 3.—Continued  
DERMATOLOGICAL CONDITIONS

	Neg.	Pos.	
Ulcer cruris .....	5	3	Three specific, five varicose ulcers.
Eczema seborrheal .....	2	0	
Tuberculosis cutis .....	1	0	
Leukoplakia buccalis .....	4	0	No history syphilis in any.
Lichen planus .....	2	0	
Sycosis .....	2	0	
Scleroderma .....	1	1	Wassermann and Noguchi both weakly positive. No history of syphilis.
Leprosy .....	0	3	
Sporotrichosis .....	1	0	
Lupus erythematosus .....	1	0	
Psoriasis .....	2	0	
Herpes zoster and progenitalis.....	5	0	
Dermatitis .....	2	0	

## NEUROLOGICAL CONDITIONS

Cerebral thrombosis; hemiplegia.....	11	1	
Cerebral endarteritis .....	3	1	
Myelitis .....	6	2	In two cases diag.=specific.
Sciatica .....	2	0	
Peripheral neuritis .....	1	0	
Trigeminal neuralgia .....	2	0	
Myalgia .....	2	0	
Neuralgia .....	5	0	
Neurasthenia and hysteria.....	15	0	
Cerebral and cerebellar tumor.....	6	0	
Abscess brain .....	2	0	
Cerebellar ataxia .....	2	0	
Tumor cord and spine.....	3	0	
Spastic and ataxia paraplegia.....	4	0	Spinal fluid positive in one case.
Specific paraplegia .....	1	2	
Optic neuritis .....	2	0	
Chorea .....	2	0	
Pachymeningitis .....	2	0	
Serous and tubercular meningitis.....	2	0	
Meningoencephalitis .....	0	2	Spinal fluid positive in both.
Myasthenia gravis .....	1	0	
Epilepsy .....	2	0	
Multiple sclerosis .....	3	0	
Mongolian idiocy, imbecility.....	4	0	
Friedreich's ataxia .....	1	0	
Progressive muscular atrophy.....	2	0	
Tabes .....	3	9	One case of suspected paresis.
Paresis .....	2	3	
Cerebrospinal syphilis .....	3	12	
Paralysis agitans .....	3	0	

TABLE 3.—Continued  
SURGICAL CONDITIONS

	Neg. Pos.		
Carcinomata and sarcomata.....	38	1	Chancre years ago in one case.
Tuberculous conditions (bones, glands, testis, peritoneum, etc.).....	17	0	
Bone conditions (osteoperiostitis, pain, abscess, osteomyelitis, multiple exostosis, peritoneum, etc.).....	17	0	Positive conditions confirmed by histological examination and subsequent course.
Rectal conditions (stricture, fistula in ano, proctitis, abscess).....	2	2	Both positive cases tertiary lues.
Thrombo-anglitis obliterans .....	30	0	
Gynecologic conditions (endometritis, ectopics, fibroids, abortions).....	6	8	Eight out of twelve women with frequent abortions and stillbirths give positive reactions.
Genito-urinary conditions (stricture, cystitis, hernia, trabecular and atonic bladder, hematoma and tumor of testis, ren mobilis, enlarged prostate, undescended testicle, hydrocele, calculus, spermatocele, impotence, orchitis).....	28	2	Both orchitis cases positive.
Eye conditions (keratitis, iritis, cyclitis, corneal opacities, trauma, ophthalmoplegia) .....	10	2	Two cases interstitial keratitis positive.
Laryngologic conditions (stenosis larynx, ulcer of throat, tuberculosis, acute laryngitis, tumor tonsil, peritonsillar abscess) .....	6	0	
Chronic synovial inflammation.....	7	0	
Operative conditions (appendicitis, goiter, tumor of lung, Paget's disease, tumor and abscess breast, liver abscess, splenomegaly, etc.) .....	15	0	
Acromegaly .....	2	0	
Polyadenitis .....	1	0	

Hemolytic amboceptor can be dried on filter-paper and will retain its strength with hardly any deterioration for at least from three to six months. After three months the paper commences slowly to lose in titer, but I have kept specimens of antihuman (and also antisheep) amboceptor dried on filter-paper and preserved in well-stoppered bottles for over six months with but slight loss in strength. Of course, each time before doing the test the exact titer of the reagent must be determined. Compared with the more rapid deterioration of the liquid reagent and the more frequent and more difficult titrations necessary, the above method has everything in its favor.

Complement cannot be dried on filter-paper and preserved for any length of time, so that it is advisable to use fresh guinea-pig serum for

the test, the animals being bled before the day's work is begun. Complement can usually be preserved for a day or two, but its availability should always be determined by a preliminary titration. Guinea-pig complement occasionally shows variations in fixation quality, so that, if possible, it is advisable to use the combined serum of two or more pigs.

The preparation of antigen extract on paper is not so simple a matter as is the preparation of amboceptor paper. The paper reagent in the hands of some workers has deteriorated within a month, occasionally becoming anticomplementary, i. e., inhibiting the action of complement. While this is not the rule with all specimens by any means, it occurs frequently enough to make it a disturbing factor, especially in smaller laboratories where fresh material may not be readily obtainable. Paper impregnated with an acetone-insoluble fraction of lipoids, however, has given fairly satisfactory results in my hands. Some specimens seemed to keep better than others, and when preserved at room temperature I found that at the end of from one to five months some of the preparations could be utilized, though in increased dosage. If the paper is preserved in pure acetone, it will not become anticomplementary in action, provided acetone-insoluble lipoids have been used in the impregnation.

I have found it very convenient to use a liquid preparation, the exact strength and dose of which can easily be determined. It has shown practically no deterioration within a period of over six months. The tissue extract prepared according to the method of Noguchi, consisting of pure lipoids, is dissolved in methyl alcohol. This solution of an acetone-insoluble fraction of tissue lipoids in methyl alcohol up to the point of saturation (about 2 per cent.) is then diluted with salt solution (about one to ten) and the proper dose determined by preliminary titration. That dose is chosen which will fix complement in the presence of a minimal quantity of known syphilitic serum but which in double dosage will not fix complement in the tube containing normal serum. In my routine work I use this liquid preparation, reserving the use of the paper for emergencies.

My experience covers the use of antigen-extracts prepared in the above manner from normal and syphilitic liver, human heart, guinea-pig heart, and beef liver. Comparative tests now going on to determine the relative values of the extracts so prepared tend to show that if well-preserved organs are extracted in the manner above outlined there is little difference to be noted. Fatty and fibrotic organs make poor extracts and should not be used.

I have just pointed out that the use of active serum is a factor influencing the outcome of the reaction in the direction of greater sensi-

tiveness. When active serum is used for the Noguchi test it should not be older than a day or two. If the serum cannot be examined soon after the blood is drawn, especially in warm weather, it should be inactivated. This is a very important point. Serum on standing becomes anticomplementary and may inhibit hemolysis either partially or completely. In the presence of complement that is not of normal strength, or of an antigen-extract that is even very slightly inhibitory, or with an hemolytic amboceptor that is below the double hemolytic dose necessary—with one or more of these factors a degree of inhibition of hemolysis may be obtained with such a serum that may simulate a positive reaction. Inasmuch as heating serum at 56 C. for thirty minutes destroys this anticomplementary property, such specimens should be inactivated by heating before examination.

When any other antigen extract than an acetone-insoluble fraction is used, it is not safe to employ active serum in the test. It has been pointed out<sup>9</sup> that complement may be fixed by certain proteids and their cleavage products in the presence of active human serum. Now, since all antigenic extracts, watery and alcoholic, contain proteins capable of causing this non-specific fixation, except alcoholic extracts that have been fractionated with acetone, fresh active serum can be used with safety only in the presence of the extract above described which contains pure lipoids.

For the various steps in the performance of the test the reader is referred to the original publications of Noguchi.<sup>1, 10</sup> It is essential to bear in mind that the controls so necessary with the original test are to be insisted on just as urgently in the test under discussion. Although the steps are somewhat easier, just as much care is necessary in each one of them. In the interpretation of results very slight degrees of inhibition should be disregarded for diagnosis. With a suspicious Wassermann, a faint to moderate degree of inhibition with Noguchi is of some significance. Thus the two test supplement and control each other. Tests should be repeated before a final result is recorded.

Certain investigators, among whom may be mentioned Swift<sup>11</sup> and Kaplan,<sup>12</sup> have reported an unusually large percentage of positive results in cases in which syphilis could be excluded with a fair degree of certainty. They used active serum in the quantity prescribed by Noguchi.

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9. *Proc. Soc. Exper. Biol. and Med.* 1910, vii, 55.

10. Noguchi, H.: *Serum Diagnosis of Syphilis*, Philadelphia, J. B. Lippincott Co., 1910.

11. Swift, H. F.: *The Use of Active and Inactive Serum in the Complement Deviation Test for Syphilis*, *THE ARCHIVES INT. MED.*, 1909, iv, 494-501.

12. *Am. Jour. Med. Sc.*, January, 1910, cxxxix, 82.

In an effort to confirm these results I have made an analysis of more than 700 cases from the wards of the Mount Sinai Hospital, examined during the past ten months. As above mentioned, the regular Wassermann system and the Noguchi modification were applied in all, and in the majority of the cases a modification of the Bauer test<sup>‡</sup> controlled the Wassermann reaction. The results are tabulated (Table 3).

It will be seen that aside from cases of syphilis and conditions in which syphilis cannot be excluded as an etiological factor, the results are practically identical. In normal conditions, these cases being commonly referred to as controls, both the Wassermann and the Noguchi reacted negatively. A bed-to-bed canvass of patients in the wards, medical and surgical, showed uniformly negative results in over one hundred cases. None of these gave a specific history. Of about fifty applicants in response to an advertisement for donors for blood transfusions only two reacted positively. Both admitted having had hard chancres. Out of thirty-five patients with malignant disease one patient reacted positively. This patient admitted having had a chancre and secondaries in his youth. A typhoid patient who likewise reacted positively also admitted an infection about twenty-eight months before. In one case of Hodgkin's disease the positive reaction was due to a coincident syphilis. One patient with diabetes insipidus gave a positive reaction with the Noguchi and the Bauer tests, the Wassermann reacting negatively on account of the presence of an excess of antisheep amboceptor. In thirteen cases of arthritis deformans, five patients gave positive reactions with the Noguchi, only one with the Wassermann. In four of the five cases there was moderate inhibition; in one a strong reaction. The latter was positive with the Wassermann method and with the Noguchi with inactivated serum, the others all going negative with heated serum. In 25 other cases of all sorts of arthritic conditions a slight degree of inhibition was noted in many. Although this was disregarded as being too faint for diagnosis, this faint degree of inhibition was so frequently present in these conditions, that I think it prudent to examine both active and heated serum in such cases. In all of the above-mentioned cases syphilis was denied in the previous history. Heckmann<sup>13</sup>

<sup>‡</sup>The tubes containing the serum to be tested, complement and antigen extract are incubated, emulsion of sheep's corpuscles added and incubated again. To the tubes showing no hemolysis or only partial hemolysis two units of artificial amboceptor are added and the tubes placed in the incubator again. After the second incubation the pressure of antisheep amboceptor is detected by the degree of hemolysis.

13. Heckman: München. med. Wchnschr., 1909, xxxi, 1588.

found out of fifteen cases of arthritis deformans, four of the monarticular and eleven of the polyarticular form, that seven reacted positively, three weakly and one suspiciously, and the remainder negatively. He concluded that not only the monarticular form of this disease but a large percentage of the polyarticular cases are syphilitic. All of this writer's cases were examined by Dr. Noguchi. In an effort to throw a little more light on this mooted subject, the examination of a larger number of cases of this type is now being undertaken.

I have examined with Dr. Noguchi sixty-three cases of scarlet fever taken at random from the wards of the Willard Parker Hospital. The children were in all stages of the disease. One patient gave a positive reaction, two a suspicious reaction. The Noguchi test alone was applied. It was subsequently learned that the child that gave a positive reaction was a congenital luetic. The other two cases could not be traced. It is, of course, known that numerous observers have reported positive reactions with the regular Wassermann system in scarlet, though recently as laboratory workers are becoming more expert in the reaction the number of such positive reactions seems to be diminishing.

In leprosy the Noguchi reaction and the Wassermann method both give fixation in a large percentage of cases of the tubercular type. There is as yet no way of distinguishing between syphilis and leprosy by the method of serum diagnosis. Fortunately the two conditions offer little difficulty clinically in differentiation. This is true of most of the protozoan diseases known to give non-specific fixation with the Wassermann reaction.

It is not my purpose to present an analysis of the various diseases and conditions examined except in so far as they bear on the question of the specificity and availability of the Noguchi modification of the Wassermann reaction. References to the cases cited, however, will show the incidence of syphilis as an etiological factor in various medical and surgical conditions under observation in a large general hospital. The results tabulated show that the antihuman method of Noguchi can be relied on to give a larger percentage of positive reactions in known syphilis, and that in non-syphilitic conditions, with the few exceptions mentioned above that apply as well to the Wassermann method, the newer method gives uniformly negative results. Thus equal dependence can be placed on the positive results obtained with the two methods.

#### SUMMARY AND CONCLUSIONS

As a result of more than a year's experience in the performance of the Noguchi and other systems of complement fixation tests for syphilis,



during which time I have examined more than a thousand specimens of blood, I am of the opinion that the claims of the originator of the anti-human system are well-founded.

The method is simple and easily carried out.

The reagents for use in the test can be prepared in stable form in central laboratories, thus putting the test within the reach of some workers who would otherwise be compelled to do without this means of diagnosis.

A comparison of the Wassermann and Noguchi systems shows that the latter is at least as sensitive as the former in the earlier stages of syphilis while in the later stages, in treated syphilis, and in the so-called metasyphilitic conditions, it is more sensitive.

The Noguchi system is specific. Either active or inactivated serum can be used provided the essential technical procedures are carefully followed. A positive reaction therefore can be interpreted as evidence of syphilis with the same degree of assurance as applies to the regular Wassermann test.

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## A STUDY OF EXPERIMENTAL CONDITIONS OF LOW BLOOD-PRESSURE OF NON-TRAUMATIC ORIGIN\*

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The study of experimental conditions of low blood-pressure has been limited for the most part to conditions of shock due to traumatism, thermic influences, or exposure, and aside from pharmacological investigations of the mode of action of certain substances such as arsenic, but few attempts to study, experimentally, low blood-pressure due to toxic agents have been made. The study of the latter should, therefore, be of interest not only to the internist, in that it may offer an explanation of conditions of collapse or shock occurring in medical as controlled with surgical practice, but also of general importance, in that it supplements the experimental work of Crile<sup>1</sup> and others on surgical shock. Such a study was suggested by the observation of Biedl and Kraus,<sup>2</sup> which we<sup>3</sup> have confirmed, that anaphylactic shock in the dog is characterized by a low blood-pressure resembling in many ways that of surgical shock. This condition, unaccompanied by mechanical injury or hemorrhage, but due to the action of horse-serum on an animal in every way normal except that it had been sensitized to such serum, appeared to us to be analogous to those conditions of suddenly developing low pressure occurring in medical, as contrasted with surgical practice, which are usually associated with a general intoxication. The close analogy between the blood-pressure changes of anaphylactic "shock" and "peptone" intoxication led us to utilize the latter also in our studies.

The main object has been to study the treatment of low blood-pressure, but in order to interpret properly the effects of treatment, it was necessary first to determine the mechanism by which the low pressure was brought about and the effect of the alteration in pressure on the general

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\* From the Carnegie Laboratory of New York University; aided by a grant from the Rockefeller Institute for Medical Research.

1. Crile, G. W.: *An Experimental Research into Surgical Shock*, 1899; *Blood-Pressure in Surgery*, Philadelphia and London, 1903; *Hemorrhage and Transfusion*, New York and London, 1909.

2. Biedl, A., and Kraus, R.: *Experimentelle Studien über Anaphylaxie*, *Wien. klin. Wchnschr.*, 1909, xxii, 363.

3. Pearce, R. M., and Eisenbrey, A. B.: *Anaphylactic "Shock" in the Dog*, *Proc. Soc. Exper. Biol. and Med.*, 1909, vii, 30.

distribution of the blood. That portion of our study which deals with the mechanism of anaphylactic shock has been presented elsewhere.<sup>4</sup> The details of the mechanism of peptone intoxication only will be presented here, but as the mechanism of anaphylactic shock is analogous to that of the peptone effect, the descriptions of the latter illustrate also the former.

#### DETAILS OF THE STUDY

The change in the distribution of the blood was first studied. All animals were under full ether anesthesia. The pressure was taken from the left femoral artery with a mercury manometer; the peptone solution was injected at body temperature, and slowly, into the right femoral vein. The changes in blood distribution have been determined by oncometric studies of the spleen, kidney and intestine, by a cannula introduced into the right common iliac vein and projecting into the inferior vena cava, by plethysmographic study of a fore limb and by a metal cylinder penetrating the cranial cavity. Each of these pieces of apparatus was connected by rubber tubing with bellows recorders allowing simultaneous records on a revolving drum. It was thus possible in a single experiment to obtain simultaneously, as was frequently done, records of the circulatory variations in the femoral artery, the iliac vein, the kidney, the spleen and the intestine, with also a record of the respiration, or any combination of these, and a record of variations in the volume of a limb, or in intracranial pressure. The temperature of the animals was maintained by a hot-water coil encircling the greater part of the trunk. A record of temperature was obtained by a thermometer in the rectum. Peptone (Witte's) was injected intravenously in the strength of 10 per cent. in 0.85 per cent. salt solution. The solution was allowed to run into the vein slowly from a burette until a sharp fall in pressure occurred. The amount necessary varied considerably, but it usually required 0.2 to 0.4 gm. per kilo to cause a fall in pressure lasting five minutes or more without upward tendency. This phase of our investigation includes ten observations.

#### OBSERVATIONS FROM THE EXPERIMENTS

It was found that "peptone" intoxication and anaphylactic "shock" are characterized by changes in the circulation which are closely analogous, except that in anaphylaxis the onset is more abrupt and the resulting condition more prolonged. In both a fall in blood-pressure, equal to

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4. Pearce, R. M., and Eisenbrey, A. B.: *The Physiology of Anaphylactic Shock in the Dog*. Jour. Infect. Dis., July, 1910.

50 to 70 mm. Hg, occurs immediately after injection. This is independent of initial change in heart action, though during the continuance of the effect the pulse-pressure is low, the result, apparently, of the small volume of blood passing through the heart. Respiratory disturbances, except in so far as they are secondary to the medullary anemia consequent on the low general pressure, are absent.

Oncometric studies show a decrease in the volume of kidney, intestine and spleen simultaneous with the fall in arterial pressure. Of these three organs the decrease is as a rule most marked in the kidney and least in the intestine. A very slight initial decrease in brain-volume has been found as well as a slight diminution in the volume of an extremity. This decreased peripheral circulation is accompanied by an accumulation of blood in the large veins of the abdomen. This has been determined by inspection of the liver and large veins, and by the observation that a cannula introduced into the inferior vena cava and connected with a water manometer shows a moderate increase of pressure equal to 6 to 10 mm. water at the time of fall in arterial pressure, with an almost immediate return to normal level as the blood becomes evenly distributed throughout the large venous trunks.

It is evident, therefore, that the important feature of the condition of low pressure here described is a loss of tone of the vessels of the splanchnic area, resulting in extreme congestion of the large venous trunks. From this condition the animal does not quickly recover, and, as will be shown later, it is not readily influenced by circulatory stimulants. It is essentially the condition frequently characterized as a "bleeding into the veins of the abdomen" and in many respects is analogous to the circulatory disturbance of surgical shock.

Our results with peptone differ somewhat from those of Thompson, in that he found by oncometric studies a secondary rise in intestine-volume. He lays much stress on the influence of gravity, the secondary rise in intestine-volume being most in evidence when the animal is placed on its side and the level of the oncometer lowered. This apparent mechanical error we have avoided by placing the intestinal and other oncometers in as nearly as possible the normal position of the organ under observation. The uniformity of our results leads us to believe that they are not affected by mechanical influences. This view is strengthened by the fact that the organ-volume closely followed the general blood-pressure, and transient changes in the latter brought about in various ways were always accompanied by changes in organ-volume. Also it may be stated that by direct inspection during the stage of low pressure the intestine showed no evidence of congestion except in the large veins; the pallor of the tissue, under such circumstances, was striking.

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5. Thompson, W. H.: Contributions to the Physiological Effects of Peptone when Injected into the Circulation, *Jour. Physiol.*, 1896, xx, 455; 1899, xxiv, 374, 396; 1899, xxv, 1; 1900 xxv, 179.

## MECHANISM OF THE PEPTONE REACTION

The mechanism of the "peptone" reaction has been studied extensively. At present we are not especially concerned with the question of the nature of the substance in preparations of peptone which causes the effect on blood-pressure.<sup>6</sup> It may be sufficient to state that the older view, based largely on the experiments of Pick and Spiro,<sup>7</sup> that the physiological effects were due not to the contained proteoses, but to impurities, has been rendered untenable by Underhill's results with purified products; also that the contradictory results depend largely on the animal used; thus the dog is found most susceptible, the cat less so, and the rabbit extremely resistant.

## MECHANISM OF CIRCULATORY CHANGES

Concerning the physiological mechanism of the circulatory changes, we have no definite experiments previous to those of Thompson, though Pollitzer had described the blood-pressure changes as due to a vasomotor paralysis affecting chiefly, if not wholly, the splanchnic region, and Grosjean, also, had ascribed to the vasodilatation the chief rôle, but believed it to be the result of a central disturbance. As the result of an extended series of experiments, Thompson concludes that the action of peptone is a direct or peripheral effect on the blood-vessels independent of the vasomotor center. This effect, he thinks, is in all probability a depression of irritability limited to the nervous segment of the neuro-muscular apparatus. His experiments include (1) division of the spinal cord and vagi; (2) excitation of the peripheral end of the cord; and (3) excitation of the divided splanchnic, the cord also being divided. Under all these conditions "peptone" caused a fall in pressure. Also it was observed in the splanchnic excitation experiments that at the period of lowest blood-pressure splanchnic stimulation gave, for a short period of time, no response.

## COMPARISON OF PEPTONE AND ANAPHYLACTIC REACTIONS

Our study by physiological methods of the mechanism of changes in pressure due to "peptone," and that associated with anaphylactic shock, includes experiments in which the spinal cord, vagi and cervical sympathetic and splanchnic nerves have been divided. The fall in pressure after peptone injection, as shown in nine experiments, is not influenced by any or all of these procedures; nor do such operative procedures have any effect in preventing the low pressure of anaphylaxis.

In order to eliminate completely any possible central factors in the production of peptone intoxication and anaphylactic shock, decapitated animals were used in addition to those having the cord, vagi, and cervical sympathetic nerves severed. Decapitation may be performed with a comparatively negligible amount of hemorrhage by clamping the common carotid arteries and the internal and external jugular veins simultane-

6. A summary of the literature to 1903 may be found in the excellent account by F. P. Underhill: *New Experiments on the Physiologic Action of the Proteoses*. *Am. Jour. Physiol.*, 1903, ix, 345.

7. Pick, E. P., and Spiro, K.: *Ueber gerinnungshemmende Agenten im Organismus höherer Wirbelthiere*, *Ztschr. f. physiol. Chem.*, 1900-01, xxxi, 237.

ously low in the neck, having first ligated the vertebral arteries at the point where they enter their canals in the transverse processes of the cervical vertebrae. After decapitation it was found that the blood-pressure fell to a point averaging one-half of its original level and was maintained there for a period covering the usual length of the experiment, if care was exercised to keep the artificial respiration uniform and to maintain the body heat. With the loss of vagus influence the heart-rate is quickened, the pulse-pressure lowered, and the respiratory waves become well marked. Under such circumstances, however, both peptone and the toxic dose of horse-serum cause a fall of blood-pressure to the level occurring from similar doses in intact animals. The onset of the fall is less abrupt, the low level is reached more slowly and the tendency to spontaneous recovery is markedly decreased.

When, in addition to decapitation, the cord is destroyed, there is a further fall in blood-pressure to a point so low that the heart suffers from lack of blood and death rapidly ensues from failure of the circulation. If, however, this extreme fall and low blood-pressure level is combated, the cardiac anemia prevented, and a circulation sufficient for the observation of changes in pressure is established by increasing the blood-volume by transfusion, it is found that the peptone and anaphylactic reactions may still be obtained. As a result of the extreme peripheral relaxation thus produced, a condition is present in which the vessels are practically a system of non-contractile tubes, cardiac anemia supervenes and death quickly ensues. This demonstrates conclusively that the peptone and anaphylactic reactions may be produced independently of the medullary and spinal centers, by an influence on a vasomotor mechanism located either in the ganglia of the splanchnic area or at the neuromuscular junction in the vessel-walls. The experiments in which the splanchnic nerves and ganglia were destroyed point to the neuromuscular junction as the seat of this action.

While these experiments on animals with the spinal cord destroyed after decapitation have shown that the usual effect on the blood-pressure may be produced without central action, such experiments do not exclude the possibility that the central vasomotor mechanism may play some part in the symptom-complex presented by intact animals. With the object of ascertaining the nature and extent of a possible central action without the complication of the known peripheral effects, we were obliged to devise a means by which the solutions used might be introduced into the cerebral circulation, but not reach the circulation of the body. A prelimi-

nary operation is performed, the details of which are described elsewhere,<sup>8</sup> whereby vascular communication between the heart and the head and neck is obliterated and the circulation in the head and neck maintained independently by transfusion from a normal animal. Following a short period of irregularity due to the temporary changes in the cerebral circulation incidental to the technic of isolation, the general blood-pressure of the recipient is maintained at a normal level and solutions may be introduced into the cerebral or into the peripheral circulations exclusively without any of the injected material reaching the other circulation. Under such circumstances the venous outflow from the cerebral circulation took place through an incision in the left external jugular vein so that following the injections the brain received normal blood only.

When peptone is injected into the cerebral circulation alone through the carotid anastomosis a lowering of the general blood-pressure occurs, but the depression is less marked and of shorter duration than when the body alone or the entire circulation is involved. Thus, to quote one experiment, the fall in pressure after intracerebral injection was only 30 mm. Hg. whereas, after an injection into the femoral vein, two minutes later, it was 72 mm., the level usually obtained in the intact animal.

When the injection is made into the circulation of the trunk alone or after recovery from the effects of the cerebral injection, it is found that the fall in pressure is more abrupt in its onset than that due to intracerebral injection, and also that the low level is maintained for a longer time. The recovery, however, occurs more quickly than in the intact animal and is apparently due to the strong constrictor impulses coming from the active medullary centers.

Similar results were obtained when horse-serum was injected into the cerebral circulation and then into the circulation of the trunk of a sensitized dog. After recovery from the slight temporary depression following the cerebral injection, the blood-pressure shows the typical profound depression of anaphylactic shock when the horse-serum is injected into the saphenous vein. This is added evidence that the peripheral mechanism plays the essential part in the condition of anaphylactic shock.

We have therefore felt justified in concluding that in both peptone intoxication and anaphylaxis the action is wholly, or in largest degree, peripheral, either on the nerve endings or on the musculature of the vessels. A number of pharmacological experiments have been made to localize the action still further. These are based on the experiments of

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8. Eisenbrey, A. B.: A Method of Isolating the Cerebromedullary Circulation. *Proc. Soc. Exper. Biol. and Med.*, 1910, vii, 113.

Dixon,<sup>9</sup> and Brodie<sup>10</sup> and Dixon with apocodein. This substance in very large doses paralyzes vasomotor nerve endings; and "when its action is complete, pilocarpin, physostigmin and adrenalin have no effect on the blood-vessels or blood-pressure, while barium and digitalis will still constrict the blood-vessels and raise blood-pressure. The first three drugs, it is therefore assumed, act on nerve-endings and the latter two directly on muscle."

As the low pressure of anaphylaxis both in its degree and in permanence resembles closely that due to apocodein, and as Thompson ascribes the peptone action to an effect on the nerve-endings, we have tested the effect of adrenalin and barium in these two conditions. The results are not conclusive. While barium causes an increase in pressure, adrenalin does likewise; in the latter, however, the rise is but slight and never equal, even if percentage values are considered, to the normal adrenalin reaction.<sup>11</sup> Assuming, therefore, that adrenalin acts through the nerve endings, it is evident that in peptone intoxication and anaphylactic shock these structures are not completely paralyzed. Their activity, however, is greatly diminished, not only as shown by the slight adrenalin action, but also by the fact that splanchnic stimulation causes a smaller rise in pressure than in the normal animal. The muscle, on the other hand, is still very active. This is shown not only by the barium effect but also by the effect of nitroglycerin, which, according to Dixon and Brodie, acts only on the muscle and in the two conditions here described causes a further fall in pressure. Furthermore, if a sensitized dog under the influence of apocodein receives an injection of serum, the typical reactions of anaphylactic shock are not obtained. In fact, the blood-pressure is raised a few millimeters by the mechanical effect of the injection and remains so for a period of about one minute, gradually returning to a point slightly below the original level after two minutes. The typical reactions to barium chlorid and nitroglycerin are obtained, but dog's urine which, as we have shown elsewhere,<sup>12</sup> acts on the nerve-endings,

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9. Dixon, W. E.: The Paralysis of Nerve Cells and Nerve Endings with Special Reference to the Alkaloid Apocodein, *Jour. Physiol.*, 1903, xxx, 97.

10. Brodie, T. S., and Dixon, W. E.: Contributions to the Physiology of the Lungs; Part II. on the Innervation of the Pulmonary Blood-Vessels; and Some Observations on the Action of Suprarenal Extract, *Jour. Physiol.*, 1904, xx, 476.

11. If adrenalin and peptone are given together the rise due to the former occurs immediately, but is cut short by the peptone effect which continues as usual. This has previously been shown by Hamburger. (Hamburger, W.: The Action of Intravenous Injection of Glandular Extracts and Other Substances on the Blood-Pressure, *Am. Jour. Physiol.*, 1904, xi, 282.)

12. See Pearce, R. M. and Eisenbrey, A. B.: The Mechanism of the Depressor Action of Dog's Urine, with Some Observations on the Antagonistic Action of Adrenalin, *Am. Jour. Physiol.*, 1910, xxvi, 26.



exerts no depressor effect and adrenalin but slight pressor effect. It is therefore evident that in these conditions of low pressure the injury to the peripheral vasomotor mechanism is one involving the nerve-endings rather than the muscle; the function of the nerve-endings, however, is not completely in abeyance.<sup>13</sup>

#### TREATMENT

From the foregoing discussion of the causation of low blood-pressure in "peptone" intoxication and anaphylactic "shock" it is evident that our therapeutic experiments have for their object the amelioration of a circulatory condition due to an action on the peripheral vasomotor apparatus and characterized by an excessive accumulation of blood in the large venous trunks of the abdomen. There is, however, this difference in the character of the low pressure due to "peptone" and that due to anaphylaxis, which must be clearly recognized in considering the results of therapeutics. Although the anaphylactic condition may be of short duration, it is usually characterized by a low circulatory condition which frequently persists for long periods of time without change and is closely analogous to the condition of shock as generally known. All changes due to treatment under such circumstances are therefore to be ascribed directly to the action of the agent employed, with but slight tendency to immediate spontaneous recuperation on the part of the animal. On the other hand, the low blood-pressure of peptone intoxication is maintained in the average intoxications for only five to six minutes, with, after that time, a gradual tendency to improvement. It resembles a condition of collapse rather than shock. Under such circumstances all treatment after the first few minutes must be considered as aiding the natural recuperative power of the temporarily embarrassed vasomotor system.

#### TREATMENT BY TRANSFUSION

The condition of the general circulation following an increase in blood-volume by transfusion, after some of the experimental procedures directed against the different divisions of the vasomotor system, serves to illustrate the importance of the rôle played by these separate divisions in the process of recovery. When a dog is decapitated and transfused, the blood-pressure rises rapidly in proportion to the duration of transfusion and is well maintained. When, however, in addition to decapitation, the spinal cord is mechanically destroyed, transfusion causes a delayed and inadequate rise that is poorly sustained. With the loss of tonic con-

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13. The experiments described were carried out on both types of low pressure and also on animals with the peptone effect added to that of anaphylaxis. The results were the same.

strictor impulses from the spinal centers, a passive dilatation of the vessels occurs and the small, slow rise in pressure obtained with even a copious transfusion does not appear until the vessels are practically distended to their full limit and is, presumably, purely a mechanical feature. Before a level is reached which is comparable to the level obtained by a similar transfusion in a decapitated animal, the distention and loss of elasticity of the vessels is so great that the heart, which is receiving an insufficient blood-supply, is unable to increase the arterial pressure sufficiently to relieve the venous congestion.

The condition of the circulation in anaphylactic shock<sup>14</sup> is in a way analogous to that of an animal with spinal cord and medullary centers destroyed. Both centers exert little or no influence on the peripheral mechanism owing to the blocking at the neuromuscular junction, and the regulatory function of the medullary centers is further influenced by the local anemia consequent on general low pressure. Consequently venous transfusion increases the dilatation of the peripheral circulation and causes an increased congestion of the splanchnic area, without materially augmenting the amount of blood going to the heart and medulla. If we compare the circulatory condition of anaphylactic shock with that of hemorrhage, we find in both a common condition—anemia of the medullary centers—but widely different conditions in the peripheral mechanism. In anaphylactic shock the latter is out of function, while in hemorrhage its regulatory power is intact, and thus is maintained a fairly efficient circulation supplying the heart and medulla, and venous transfusion under such circumstances causes a rapid return to normal. In anaphylactic low pressure, on the other hand, such transfusion increases the splanchnic congestion without aiding the heart or the medulla. It is evident, therefore, that the two conditions to be combated are (1) the congestion of the splanchnic area and (2) the anemia of the heart and medulla. As preliminary experiments showed that drugs have little or no power to overcome both conditions, we resorted to arterial transfusion to relieve the second, and in some experiments, have bled simultaneously from the central end of the femoral veins, to reduce the splanchnic congestion.

This combination has been most successful. Bleeding from the femoral vein removes from the great veins of the abdomen a large amount of blood containing accumulated toxic products and also allows the relatively fresh blood of arterial transfusion to come in contact with the splanchnic vessels, thus presumably hastening the recovery of the per-

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14. The peptone intoxication, although analogous, is not strictly comparable on account of the tendency to gradual spontaneous recovery.

ipheral vasomotor mechanism. At the same time the transfusion (by carotid anastomosis) brings a large volume of fresh arterial blood directly to the capillaries of the medulla and the heart,<sup>15</sup> and hastens their recovery before materially adding to the volume of the blood in the large venous trunks of the splanchnic area. This combination of venous bleeding and arterial transfusion is efficacious in both peptone intoxication and anaphylactic shock, and readily brings about a condition of stable equilibrium. On the other hand arterial transfusion, alone, of moderate degree, has been sufficient to bring about a restoration of pressure with maintenance at the original level, but the danger of over-transfusion and cardiac breakdown is greater.

These observations demonstrate conclusively the importance of the part played by the medullary centers in recovery from conditions of low blood-pressure.<sup>16</sup> This has been well illustrated in the work with an isolated cerebral circulation, when, with these centers unaffected by the depressing agent, and having a constant independent blood-supply, the duration of low blood-pressure, following the intravenous injection into the trunk of peptone or the anaphylactic dose of horse-serum, was markedly decreased and the recovery was more rapid than is the case in the intact animal.

These results, successful as they are in experimental procedure, can hardly be recommended as a basis for similar therapeutic measures in treating low blood-pressure in man. They do, however, offer a very satisfactory basis for the experimental study of the influence of drugs and other remedial agents.

#### TREATMENT BY DRUGS

Since in peptone intoxication the blood-pressure tends to rise spontaneously after ten to fifteen minutes, even when large doses are given, the attempts to overcome the effects of peptone by therapeutic measures have been confined to the period when spontaneous recovery was not to be expected. We have assumed that if within a period of five minutes after the production of peptone intoxication the blood-pressure could be raised and sustained at the normal level throughout the usual period of

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15. Anastomosis of a carotid of the donor to the central end of a carotid of the recipient allows, on account of the low pressure in the latter, the direct passage of blood not only to the brain of the recipient through the other carotid, but also to the coronary arteries, thus directly supplying the capillaries of the heart muscle.

16. Crile, G., and Dolley, D. H.: On the Effect of Complete Anemia of the Central Nervous System in Dogs Resuscitated After Relative Death. *Jour. Exper. Med.*, 1908, x, 782.

peptone action, a satisfactory line of treatment for this and analogous clinical conditions would be indicated.

With this end in view we have employed normal saline solution, adrenalin, caffein, digitoxin and strophanthin. These were administered through a cannula in the saphenous vein, with due regard to the temperature of the solutions and the rate of injection.

It has been found that saline solution has its usual effect, proportionate to the amount injected, of mechanically raising the pressure which, however, is not well sustained owing to the rapid passage of the fluid into the tissues. The administration of cardiac stimulants simultaneously while causing increased heart action in the usual degree and a still further rise in pressure, do not suffice to offset the loss of the mechanical effect of the saline.

Adrenalin in therapeutic doses in normal saline solution causes the most satisfactory rise in the blood-pressure and, with it, a heart action quite comparable to that obtained before the administration of the peptone. This improvement, however, is limited by the duration of the adrenalin action. Again, the simultaneous administration of cardiac stimulants causes a further rise and a more prolonged effect, but, as the constrictor effect of the adrenalin wears off, the blood-pressure again returns to a low level. During the maximal peptone action the rise of blood-pressure following adrenalin administration is small and transient even on a percentage basis. But if such administration is made late in the peptone action when the vasomotor endings are recovering and the condition of the medullary centers is likewise improving, even though the pressure is still low, the rise is proportionately greater, and subsequently the general pressure is sustained at a normal level.

The response to cardiac stimulation, in so far as the heart itself is concerned, is quite as active and as well within the normal limits as before the administration of peptone, but owing to the peripheral dilatation and the diminished volume of blood reaching the heart, the slight improvement in the general blood-pressure which ensues is quite transient. The heart shows the effect of overaction due to insufficient blood-supply, its contractions weaken and the blood-pressure quickly returns to or below the former level. If, however, as with adrenalin, such treatment is instituted toward the end of the peptone action, the recovery is much hastened and the heightened blood-pressure, due to the increased heart action, is well sustained.

While we are unable to directly neutralize the effect of the peptone intoxication or to activate the peripheral vasomotor mechanism, and are convinced of the futility of attempting to combat the condition by cardiac

stimulants alone, the results obtained by the employment of a slow, continuous injection of adrenalin in salt solution (1-40,000), administered intravenously, with the addition of a pure cardiac stimulant such as digitoxin, thus promoting the determination of blood to the right heart and an increased circulation in the brain, lead to the conclusion that a similar line of treatment is indicated in those clinical emergencies that present an analogous circulatory condition. Such treatment is not, however, specific or curative, except in so far as it serves to tide over successfully the critical period, until the effects of the toxic agent have worn off and the normal functions of the vasomotor mechanism are resumed. This has been satisfactorily demonstrated in the more prolonged condition of anaphylactic shock in which, as during the early stage of peptone intoxication, adrenalin has a minimal effect, and in which, likewise, cardiac stimulants alone are unable to overcome the effects of the paralysis of the vasomotor nerve-endings. On the other hand, a combination of the peripheral constrictor effect of a slow continuous injection of adrenalin, of salt solution and of an active cardiac stimulant, brings the circulation within the normal limits long before spontaneous recovery could be expected to occur, and maintains it at this level.

#### SUMMARY

Anaphylactic shock and peptone intoxication are characterized by conditions of low blood-pressure very similar to those seen in shock and collapse, and, as they are produced without trauma or other factors usually concerned in the etiology of surgical shock, are of interest in the study of conditions of shock occurring in medical as contrasted with surgical practice.

Both conditions are characterized by a fall in blood-pressure to a level of 20 to 30 mm. Hg, which is prolonged in anaphylactic shock, but tends to relatively rapid recovery in peptone intoxication. In both conditions there is an extreme congestion of the large venous trunks of the splanchnic area with a coincident medullary anemia. The respiration is not altered except in as far as it is affected by the anemia of the medullary centers; the heart shows no initial changes, the low pulse pressure being due apparently to the small amount of blood passing through it.

Physiological studies having for their object the determination of the mechanism by which the low pressure is caused, demonstrate that the condition is essentially a peripheral vasomotor paralysis. Pharmacological studies indicate that the effect is on the nerve-endings rather than on the muscle.

With independent cerebral transfusion the recovery from low pressure is more rapid than in the intact animal. This is true also when an animal is transfused by carotid anastomosis, and recovery is especially satisfactory when the transfusion is accompanied by simultaneous bleeding from the femoral vein.

The indications for treatment, therefore, appear to be (1) relief of splanchnic congestion and (2) increase of volume of blood to the heart and medulla. Cardiac stimulants alone, or salt solution or adrenalin alone, cannot bring about a permanent improvement. A combination, however, of the slow injection of adrenalin in salt solution (1 to 40,000) intravenously with the addition of a pure cardiac stimulant, as digi-toxin, leads to relatively rapid and permanent improvement, by promoting a determination of the blood to the right heart and increasing the circulation in the brain.

The results of the experimental treatment of this condition, which, for want of a better name, may be called toxic shock, are not essentially different from those in traumatic shock.

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## BOOK REVIEWS

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**MEDICAL ELECTRICITY AND ROENTGEN RAYS.** By Sinclair Tousey, A.M., M.D., Consulting Surgeon to St. Bartholomew's Clinic, New York City. Octavo of 1116 pages, with 750 illustrations. 16 in colors. W. B. Saunders Company, Philadelphia and London, 1910. Cloth, \$7.00 net; half morocco, \$8.50 net.

Probably no chapter in medical history is more remarkable than the one related to electricity and radiography as applied to the treatment and diagnosis of human ills. Of all the works which have come to our notice on this subject, Dr. Tousey's book is the most complete and satisfactory.

The author in his preface under date of April, 1910, makes the following statements which indicate how rapidly this important topic is growing. "Now that the work approaches completion the author realizes that it is impossible for any book on electricity to be up to date. A weekly magazine would be more apt to justify this title in the case of a science which is developing so rapidly and along such important lines. A systematic attempt to present what has been done and of how to do it may, however, prove useful."

Where a statement is ascribed to some particular observer, this is done either because the statement has not yet been verified by universal experience or in order to give due credit to the discoverer of an established fact. The radiographs in this book were made by the author except where otherwise stated, and the technic employed is one available for the average practitioner who desires uniformly successful results.

**THE PANCREAS: ITS SURGERY AND PATHOLOGY.** By A. W. Mayo Robson, D.Sc., F.R.C.S., London, and P. J. Cammidge, M.B.D.P.H., London. Octavo, 546 pages, illustrated. W. B. Saunders Company, Philadelphia and London, 1907.

The scope of this work is far broader than its title implies. The authors deal very fully with the anatomy, comparative anatomy, embryology, histology, physiology, pathology and chemical pathology of the pancreas, and then take up the general symptomatology and diagnosis, followed by a discussion of injuries to the gland, and its diseases. In the general part of the book the diseases of the pancreas are all described at great length and from every point of view, and again, in quite as much detail, in the special part. This needless repetition swells the book to about twice its natural size.

The clinical and surgical part of the book is excellent. Robson, it will be remembered, was a pioneer in the surgery of the pancreas, and the fruits of his wide experience are well displayed. Too much credit cannot be given him for his discovery of the frequency of chronic pancreatitis and its curability by operation. He was the first to show that chronic pancreatitis exists in a large proportion of cases of impaction of gall-stones in the common duct, and that this condition can be cured by removal of the stones, with drainage of the bile passages. He also showed that chronic pancreatitis, by pressure on the pancreatic portion of the common duct, may be a cause of long-continued jaundice in the absence of gall-stones, and that this condition also is curable, if not allowed to go too long without operation, by drainage of the bile-passages (by cholecystotomy, or preferably by cholecystenterostomy). He operated in 102 cases of chronic inflammation of the pancreas, with 96 per cent. of recoveries, a truly brilliant result.

Exception may be taken to some of Robson's statements, as for instance when he says (p. 312) that in thin persons the normal pancreas can be readily palpated, and that the hemorrhagic tendency can be "successfully combated" by the admin-

istration of calcium salts (p. 462). His remark that many cases of simple catarrhal jaundice are really due to catarrhal pancreatitis is a pure assumption, in support of which he brings no reliable evidence. His conception of acute "pancreatitis" as an inflammatory affection is probably erroneous, the weight of evidence being now in favor of a preliminary necrosis of the pancreas, followed by hemorrhage, and frequently by infection of the necrotic tissue. In fact, many of the so-called "abscesses" of the pancreas show on examination, not pus, but detritus resulting from the breaking down of tissue. Nor is it probable, as he assumes, that hemorrhage into the pancreas is the first phenomenon in any considerable proportion of the cases.

The chemical portion of the work is less satisfactory. A tremendous stress is laid throughout on the "Cambridge reaction," which has been shown by a number of workers to be practically valueless in all its modifications. Cambridge, however, deserves credit for the discovery of this reaction, which is of considerable theoretical interest. The method he recommends for the clinical estimation of fat in the feces is too inexact to be of much use. He determines, very roughly, first the total fat, and then the neutral fat plus fatty acids, the soaps being estimated by subtracting the second result from the first. His terminology is also confusing, for he alludes to the figure representing neutral fat plus fatty acids as "neutral fat," while the soaps he calls "fatty acids." The total amount of fat-splitting is not determined at all.

The illustrations are numerous, and with the exception of many of the photomicrographs, excellent. Taken as a whole, this is the most thorough book that has been written on the subject, and can be heartily recommended to all those interested in the diseases of the pancreas.



# PATHOLOGY AND BACTERIOLOGY OF ACUTE ANTERIOR POLIOMYELITIS\*

H. E. ROBERTSON, M.D.

AND

A. J. CHESLEY, M.D.

MINNEAPOLIS

## I. PATHOLOGY

BY H. E. ROBERTSON, M.D.

Our knowledge of the pathology of anterior poliomyelitis dates from 1863, at which time Cornil<sup>1</sup> published the report of an autopsy on a patient who died at the age of 49, forty-seven years after the acute attack. He noted the loss of nerve-cells and atrophy of the affected muscles. Two years later Prevost<sup>2</sup> described an autopsy on a still older case in which he found loss of nerve-cells, overgrowth of neuroglia, and asymmetry of cord, with reduction in the size of the left ventral horn.

Johnson and Clarke,<sup>3</sup> in 1868, from a study of the spinal cord of a man aged 32, who had suffered his acute attack in early infancy, advanced the opinion that atrophy of the nerve-cells is the cause of changes in the voluntary muscles. A similar case led Charcot and Joffroy,<sup>4</sup> in 1870, to state that the ventral nerve-cells are first and specifically involved, as in progressive muscular atrophy, but more suddenly. These conceptions were based entirely on examination of old healed lesions, with no reported observations of initial stages, and yet for many years they were widely quoted in favor of the theory that the disease is essentially a primary degeneration of the anterior horn cells.

The following year, 1871, Roger and Damaschino,<sup>5</sup> after a careful review of the literature to date, reported three cases in children with autopsies two, six, and thirteen months after the onset of the disease.

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\*Joint studies in the laboratories of the Minnesota State Board of Health and the Department of Pathology and Bacteriology of the University of Minnesota, under the direction of E. F. Westbrook.

1. Cornil: *Compt. rend. Soc. de biol.*, 1863, 187.

2. Prevost: *Compt. rend. Soc. de biol.*, 1865, p. 215.

3. Johnson and Clarke: *Med. Chir. Tr.*, London, 1868, li, 250.

4. Charcot and Joffroy: *Arch. de physiol. norm. et path.*, 1870, iii, 134.

5. Roger and Damaschino: *Gaz. méd. de Paris*, 1871, xxvi, *Compt. rend. Soc. de biol.*, 1871, 49.

From these studies they concluded that the primary lesion in the cord is vascular and the process an inflammatory softening, of the nature of a myelitis.

The first report of an autopsy on an adult patient, a woman of 67, was published by Gombault,<sup>6</sup> in 1873. Death occurred seven years after the acute attack. There was involvement of the anterior horns and



Fig. 1.—Cord (Case 1): anterior horns showing deep congestion, infiltration and edema.

some degeneration of the anterior nerve-roots. The lesion was not regarded as primarily inflammatory, thus agreeing with the opinion of Charcot. In a case in which the patient died at the age of 23, twenty

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6. Gombault: *Arch. de physiol. norm. et path.*, 1873, v, 80.

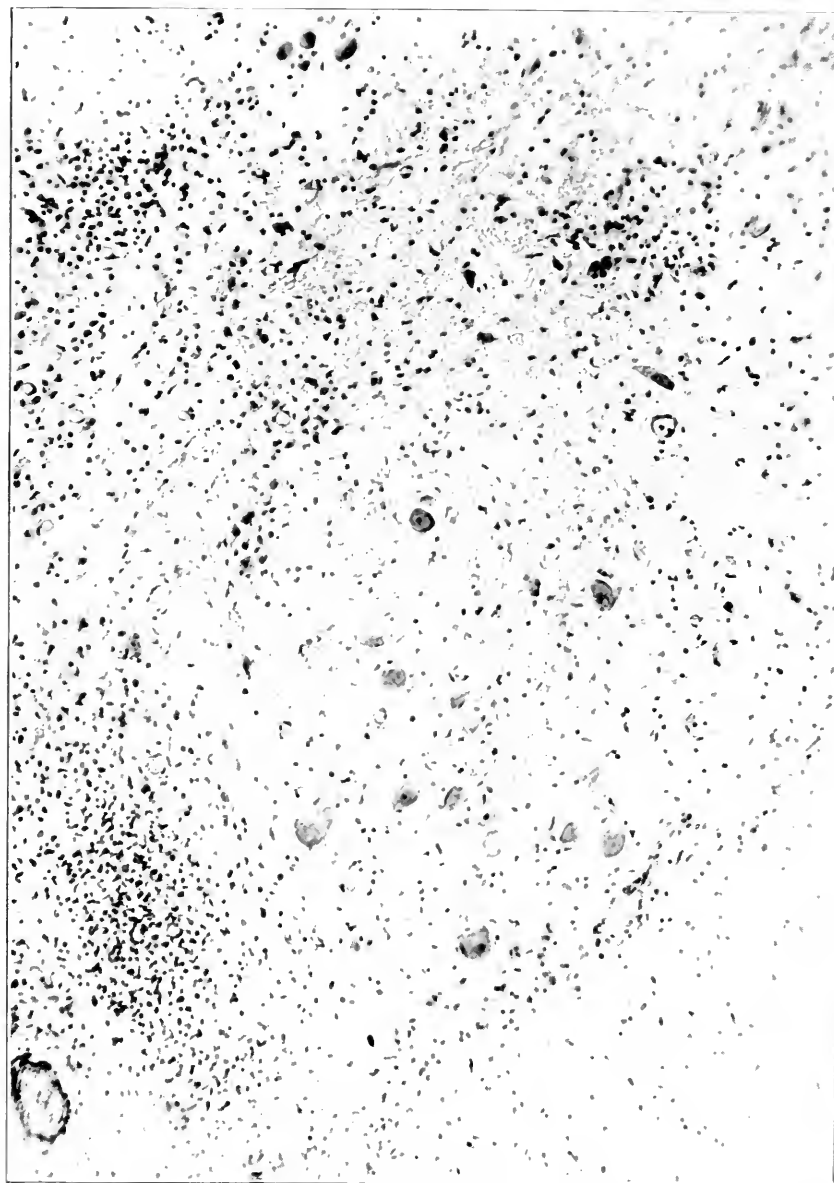


Fig. 2.—Cord (Case 1): a zone of infiltration surrounding a group of degenerating ganglion cells which show peripheral arrangement of Nissl's bodies.

years after the acute attack, F. Schultze<sup>7</sup> found changes in the lateral tracts and Clarke's columns in addition to the usual lesions. With Roger and Damaschino he regarded the process as inflammatory in type. Déjerine,<sup>8</sup> in 1878, by studies on two cases in children with autopsies, supported Charcot's view of the parenchymatous nature of the disease.

In 1883, Archambault and Damaschino,<sup>9</sup> in their autopsy, found "red softening" in the anterior horns. Two years later Drummond<sup>10</sup> published a description of the cord from a child with death about seven hours after onset. The ventral horns were congested and showed minute hemorrhages. Microscopically there was leukocytic infiltration and the nerve-cells were swollen, granular, and ill-defined. The following year



Fig. 3.—Cord (Case 2): hemorrhage and cellular infiltration in anterior horns.

Money<sup>11</sup> studied two cases with autopsies, and first called attention to the presence of thrombosis in a vessel in the anterior horn.

Rissler's<sup>12</sup> opportunity was exceptional. His material was from five cases, three early (one an adult with death on the eighth day), and two late. In his paper, appearing in 1888, he concludes that in acute cases

7. Schultze, F.: *Virchow's Arch. f. path. Anat.*, 1876, lxxviii, 128.

8. Déjerine: *Progrès méd.*, 1878, v, 423.

9. Archambault and Damaschino: *Rev. mens. d. mal. de l'enf.*, 1883, i, 63.

10. Drummond, D.: *Brain*, 1885, viii, 14.

11. Money: *Tr. Path. Soc. London*, 1884, xxxv, 45.

12. Rissler, J.: *Nord. med. Ark.*, 1888, xx, 1.

there is cellular infiltration and degeneration of nerve-cells, but, with Charcot, he believes the nerve-cell changes are primary.

Marie<sup>13</sup> advanced the opinion that an infectious embolism or thrombosis in one of the branches of the anterior median artery may be the starting point of the disease.

In 1893 Goldscheider<sup>14</sup> published the best review of the literature to date. Contrary to Charcot he believes that the primary condition is a congestion of the central arteries of the cord followed by diapedesis and infiltration of the surrounding nervous tissue by small cells and serum. This choking of the gray matter by inflammatory products causes impoverished nutrition and actual disintegration of the nerve-cells of the ante-

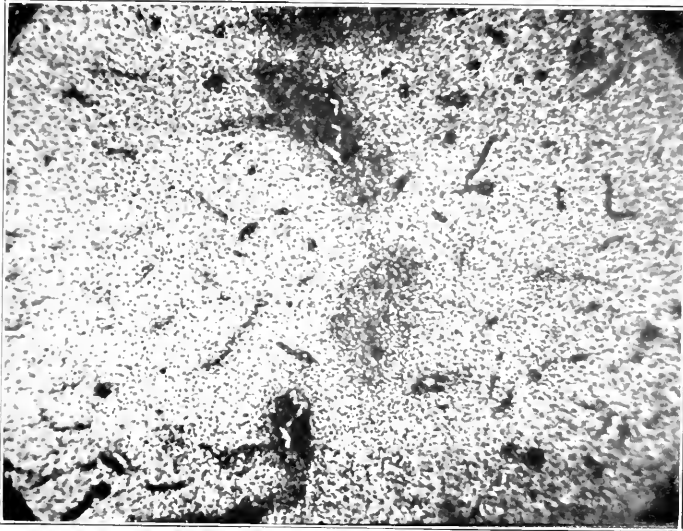


Fig. 4.—Enlarged view in anterior horns of cord shown in Figure 3.

rior horn, with ensuing permanent destruction of the nerve-tissue. He suggests that, in acute anterior poliomyelitis, substances giving rise to cell proliferation affect the walls of the blood-vessels by filtration and diffusion from the blood. In this connection Woodhead<sup>15</sup> points out that the endothelial cells of the cerebrospinal system of capillaries are extremely delicate and active; the lymph flow is great; and if the products of bacteria, or bacteria themselves, have any effect on the walls of the blood-vessels they should manifest themselves here, and we should expect to find

13. Marie: *Leçons sur les maladies de la moelle*, Paris, 1892.

14. Goldscheider: *Ztschr. f. klin. Med.*, Berl., 1893, xxiii, 494.

15. Woodhead: *Williamson's Diseases of the Spinal Cord*, London, 1908.

well-marked vascular and perivascular interstitial changes. Owing to the greater blood-supply the toxin will be brought into closer relationship with the gray matter than the white.

The following year Siemerling,<sup>16</sup> from studies of two cases in infants, with autopsies, stated that "in the pathogenesis of infantile paralysis, the inflammatory lesion of the interstitial tissue with a distention of the anterior spinal arteries plays the chief rôle. A primary inflammation of the ganglion cells in the sense given by Charcot is not to be admitted."

Bruins and Windschied<sup>17</sup> conclude that the disease is an interstitial myelitis of the gray matter of the anterior horns, having its origin in the blood-vessels. Starr<sup>18</sup> apparently also supports this view.



Fig. 5.—Cord (Case 3): hemorrhages and infiltration of anterior horns.

In 1898, Greene, Wilson and Rothrock<sup>19</sup> reported an autopsy on a woman aged 20, who, after a five days' acute illness with rapid ascending paralysis, showed involvement of the respiratory muscles, and for forty-one days was kept alive by artificial respiration. They believed that the

16. Siemerling: *Arch. f. Psychiat.*, 1894, xxvi, 267.

17. Bruins and Windschied: *Twentieth Century Practice of Medicine*, xi, 688-9.

18. Starr: *Albutt's System of Medicine*, viii, 196.

19. Greene, Wilson and Rothrock: *Philadelphia Med. Jour.*, 1898, ii, 1181.



Fig. 6.—Cord (Case 3), showing involvement of both anterior horns.

pathological process was an ascending inflammation of the gray matter of the anterior horns, and extra-vascular in origin.

Taylor,<sup>20</sup> in 1902, published an important paper on "Polio-myelitis in the Adult," giving the report of one case coming to autopsy, and a careful review of the entire literature. He concludes that poliomyelitis is an infection of undetermined character limited to the region of the ventral horns of the cord, and that the pathological alterations found are consistent with the theory of primary inflammation acting in the general distribution of the arteries of the cord and a secondary destruction of nerve-cells.



Fig. 7.— Enlarged view of one side of cord shown in Figure 6 showing hemorrhage.

Two years later Batten<sup>21</sup> reported careful studies of the material from an autopsy on an acute case. From these he forms the opinion that the pathological changes in the anterior horns are due to a "primary thrombosis of a branch or branches of the anterior spinal artery supplying the gray matter. Such thrombosis may be produced by many and various forms of infection, or, in other words, the disease is not due to a special specific infection."

20. Taylor: Jour. Ment. and Nerv. Dis., 1902, p. 449.

21. Batten: Lancet, London, Dec. 20, 1902, p. 1677.



Bruining<sup>22</sup> is one of the few recent writers who supports Charcot's views. His conclusions are based on material from a case coming to autopsy two years after the acute attack. He found the vessels congested but no perivascular infiltration. From the absence of any inflammatory changes he believes the disease attacks the nervous elements primarily.

Hock<sup>23</sup> studied the tissues from an acute case, the patient dying thirteen weeks after the onset. He summarizes his conclusions as follows:

1. Anterior poliomyelitis is the result of a primary inflammatory disease of the blood-vessels of the cord which may be thrombotic or embolic.

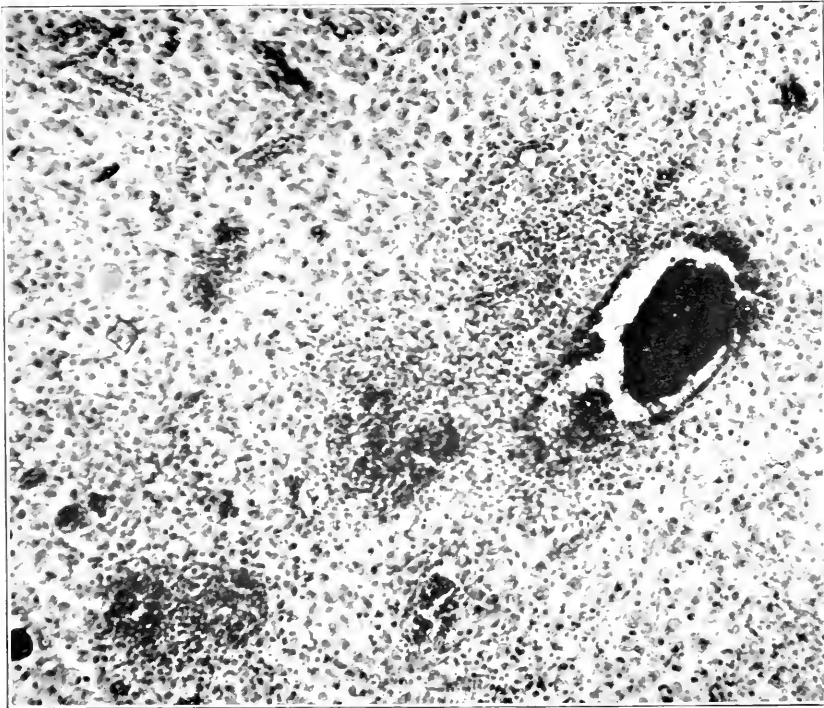


Fig. 8.—Area in Figure 7, showing hemorrhage in anterior horn with appearance of thrombosis.

2. The destruction of the ganglion cells is secondary and depends in part on the deficient blood supply of the diseased area and in part on pressure and toxins.

3. The inadequate collateral circulation within the anterior horns is favorable for sluggish circulation.

Wickman,<sup>24</sup> in 1905, published an extensive monograph. His pathological material was from nine cases, seven recent and two late. He

22. Bruining: *Ztschr. f. Nervenhe.*, 1904, xxvii, 269.

23. Hock: *Jour. Ment. and Nerv. Dis.*, September, 1905, p. 545.

24. Wickman: *Studien über Poliomyelitis acuta*, Berlin, S. Karger, 1905.

believes that the process is an infiltrative disseminated myelitis, the infiltration lying in close connection with the blood-vessels. He found no evidence of embolism or thrombosis. While the interstitial and parenchymatous changes ran about a parallel course, ganglion-cell degeneration alone was not observed, but often he found normal cells in the neighborhood of altered vessels. He is inclined to regard the mode of infection as lymphogenous and suggests that it seems probable that the pathological

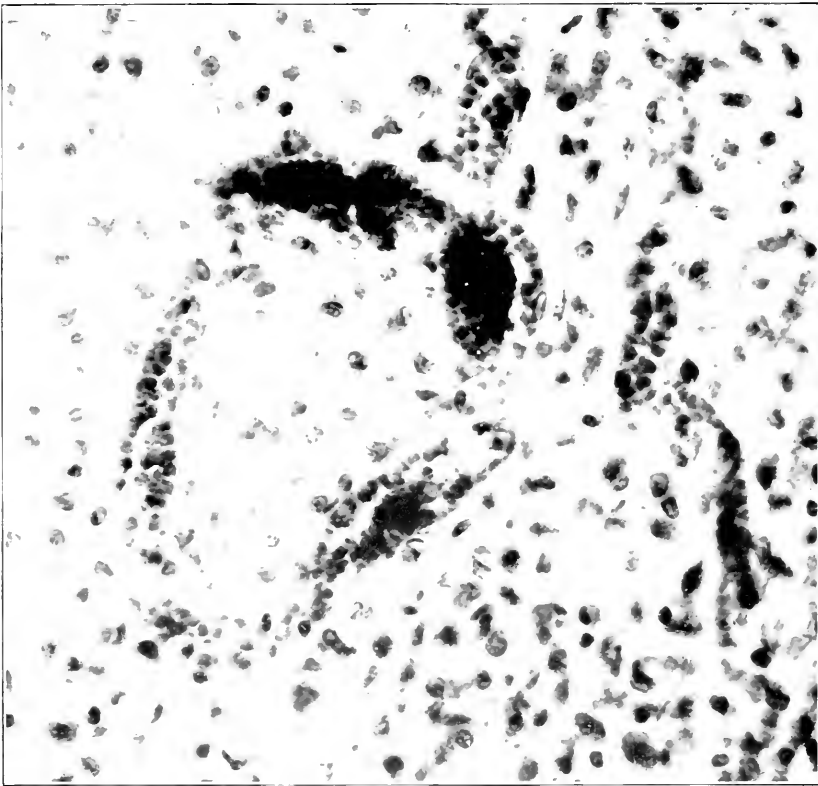


Fig. 9.—Area in Figure 7, showing dilated capillaries with stasis.

condition found in poliomyelitis may be due to a poison similar to that of rabies.

Writing in Osler's "Modern Medicine," Buzzard<sup>25</sup> summarizes the changes as follows:

1. Congestion of all blood-vessels of the cord and packing of the adventitial sheaths and lymph-channels with cells.

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25. Buzzard: Osler's Modern Medicine, Philadelphia and New York, vii, 261.



Fig. 10.—Cord (Case 3), showing hemorrhage into anterior horn of one side and perivascular groups of cells in white matter.

2. An intense proliferation or exudation of cells limited almost entirely to the gray matter of the anterior horns.
3. Round-cell infiltration of the soft meninges.
4. Retrograde (secondary) changes in those nerve cells and fibers which are intimately involved in the areas of inflammation.

By far the most important contribution to this subject has been made by Harbitz and Scheel<sup>26</sup> in a monograph published in 1907, in which they report the results of studies on material from nineteen autopsies, grouped as follows:

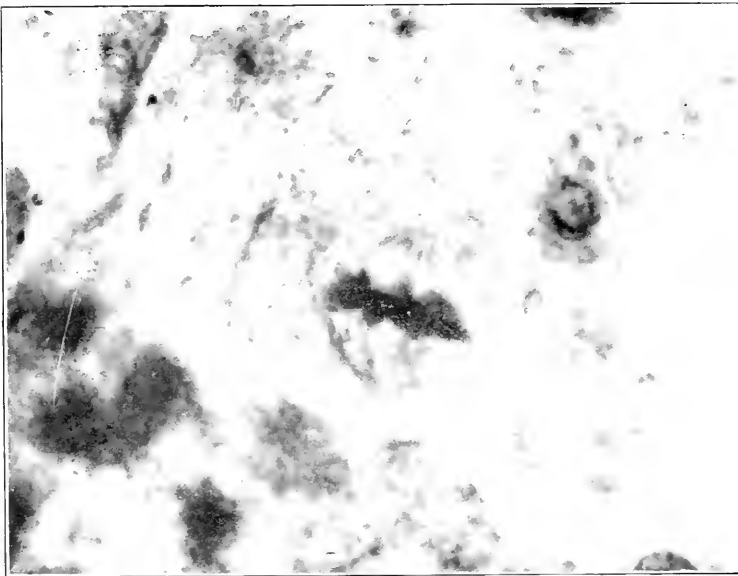


Fig. 11.—Endothelial cells in mitosis, found within circle of Figure 10.

1. Thirteen cases of acute poliomyelitis with death from two to ten days after onset.
2. Four cases with death from one and one-half to twenty-two and one-half months later.
3. Two cases of acute encephalitis.

They believe that the disease begins as a primary inflammation of the pia mater extending into the cord and producing a diffuse infiltrating inflammatory lesion closely related to the blood-vessels and chiefly in the gray matter of the anterior horns. They describe the cellular infiltration as consisting "partly of small and large mononuclear lympho-

26. Harbitz and Scheel: *Pathologisch-anatomische Untersuchungen über akute Poliomyelitis und verwandte Krankheiten von den Epidemien in Norwegen 1903-1906*. Christiania, 1907.

cyte-like cells, especially in the pia mater and white substance, and partly of polymorphonuclear leukocytes, particularly in the gray substance." The degeneration of the ganglion cells was marked, their remnants often being surrounded by heaps of leukocytes (neuronophages). The inflammation often had a hemorrhagic character, especially in the anterior gray horns. No mention is made of thrombosis or embolism.

B. Sachs,<sup>27</sup> at the last meeting of the Association of American Physicians, emphasized the toxic character of the disease process, its vascularity of origin and its tendency to involve the whole cord, and yet to expend its chief force on the ganglion cells of the anterior horns. He notes the evidences of sepsis in liver, spleen and thymus and the tendency to bronchopneumonia.

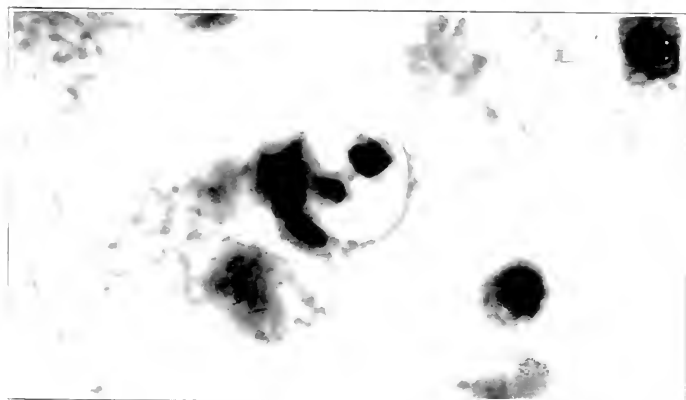


Fig. 12.—Endothelial cells inclosing nuclear fragments, found within circle of Figure 10.

In this review of the literature on the pathology of poliomyelitis we have found records of about 100 autopsies, nearly one-half of which have been performed on old cases.

#### REPORT OF CASES

Our own studies include material from six autopsies performed on cases occurring in the Minnesota epidemic of 1909.<sup>28</sup> They will be considered in the order of the respective ages of the patients.

27. Sachs, B.: Pathology of Poliomyelitis, Jour. Am. Med. Assn., 1910, liv, 1807.

28. These studies have been made possible through the courtesy and co-operation of attending physicians and associated medical and health officials.

CASE 1.—Baby boy, aged 9 months. Acute febrile attack followed by flaccid paralysis of upper and lower extremities. Death on fourth day.

*Autopsy.*—Aug. 10, 1909, nine and one-half hours post mortem. Body is that of a normally developed, well-nourished male infant. Peritoneal, pleural and pericardial cavities normal; heart muscle pale and soft. There is a minute slit-like opening in foramen ovale. Lungs in the dependent portions are dark in color and heavy with congestion. Anterior inner margins expanded and feathery. No evidence of pneumonia. Spleen is soft, swollen and dark in color. On section, pulp scrapes away readily, lymph nodules are prominent and surface deeply con-

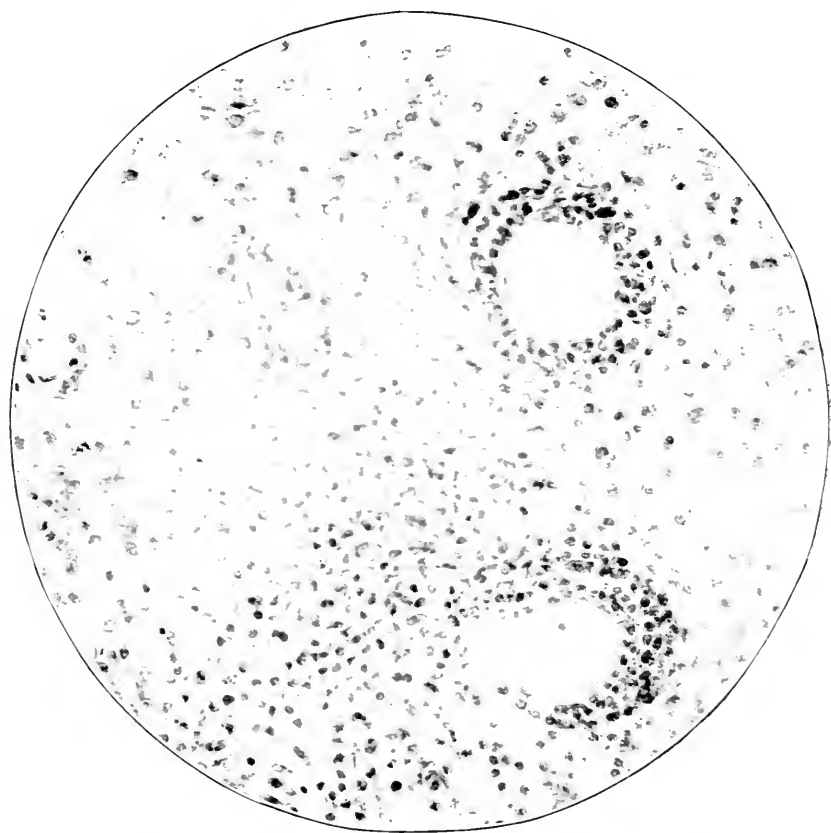


Fig. 13. Perivascular collection of cells with beginning diffuse infiltration (Case 3).

gested. Liver shows cloudy swelling. Pancreas and stomach normal. Mucosa of intestinal tract shows several widely separated areas of deep congestion. Adrenals normal. Kidneys congested, swollen and cloudy. Bladder and genital organs normal. Epiglottis, pharynx, larynx, and trachea free from congestion or evidence of exudate. Thymus weighs 25 gm., is grayish pink in color and from cut surface a small amount of milky fluid escapes on pressure. Head normal to external examination. On removing calvarium and reflecting dura, vessels of pia-

arachnoid are deeply congested. No increase of fluid in subarachnoid space. Brain removed with cord attached. Middle ears and bony air spaces normal. Careful section of brain shows no demonstrable lesion of cerebrum, lateral ventricles, cerebellum, basal ganglia or pons. Vessels of pia-arachnoid of cord deeply congested. No increase of spinal fluid, which is clear. Membranes free from exudate. In the lower portion of the medulla on the transversely cut surface is a softened area with a pin-head hemorrhagic center in the gray matter of the right side. Serial transverse sections of the cord, about 1 cm. apart, show numerous similar softened, hemorrhagic areas in the gray matter of the anterior horns. In passing down the cord they alternate fairly uniformly from one side to the other as far as the lumbar swelling, where hemorrhages appear on both sides. They average about 3 mm. in length and are most pronounced in the cervical and lumbar swellings. The cord shows swelling and softening of the affected sides.

*Autopsy Diagnoses.*—Acute hemorrhagic anterior poliomyelitis. Congestion of pia-arachnoid of cord and brain. Congestion of spleen and lungs. Cloudy swelling of liver and kidneys. Partially patent foramen ovale.



Fig. 14.—Anterior horns of cord (Case 4), showing advanced destruction of gray matter.

*Histological Examination.*<sup>29</sup>—Heart: Slight edema of connective tissue with swelling of muscle fibers. Lungs show dilated and congested vessels. Spleen: Blood-sinuses congested. Lymph-sinuses distended by lymphoid and proliferated endothelial cells. Malpighian bodies prominent and centers contain masses of endothelial cells, many of them phagocytic for other cells, nuclear fragments, and brown pigment. Liver: Edema of stroma and granular and vacuolar degeneration of pulp-cells. Sudan III stain in frozen sections shows extensive fatty changes. Colon normal. Kidney: Epithelial cells of tubules, especially the convoluted, swollen and lumina contain small amounts of precipitated serum. Capillary tufts of glomeruli and veins congested. Capsule and interstitial tissue

29. Unless otherwise stated sections were prepared by imbedding in celloidin and staining with hematoxylin and eosin.

edematous. Peribronchial lymph-node shows changes similar to those in the spleen, the phagocytosis being particularly marked. Thymus: Hyperplasia of lymphoid elements. Dilated sinuses filled by lymphoid and endothelial cells; Hassall's corpuscles markedly degenerated, taking the eosin stain strongly and surrounded by a connective tissue sheath giving the appearance of lymph-sinuses thrombosed by masses of necrotic cells. Pituitary shows congestion of vessels of both lobes and dilatation of interlobar lymph-channels. Cerebrum and cerebellum, aside from congestion, especially of pial vessels, free from evidence of lesion.

Basal Ganglia: One vessel found with outer sheath containing polymorphonuclear leukocytes and lymphoid cells.

Medulla: In upper portion vessels uniformly congested. Perivascular lymph-channels located beneath the ependymal surface of fourth ventricle are distended

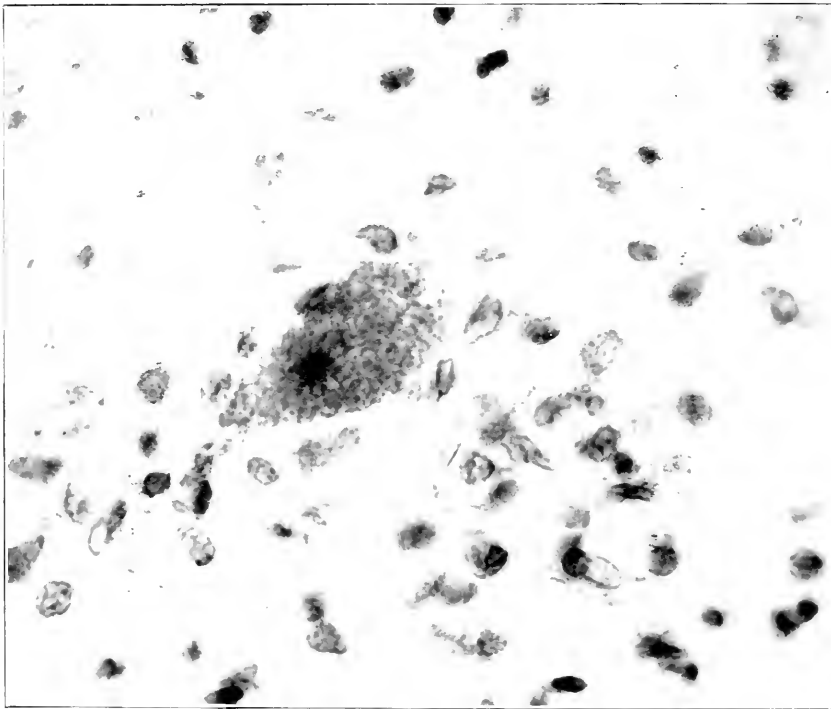


Fig. 15.—Degenerating ganglion cell with beginning giant cell formation (Case 4).

and packed with lymphoid and endothelial cells, the former in predominance. Many of the ganglion cells in this region are in various stages of degeneration, some showing peripheral arrangement of Nissl bodies with a clear perinuclear zone, others with faint staining nuclei and a swollen, granular, homogeneous cytoplasm, and still others showing loss of nucleus and beginning disruption of cell. Small foci of infiltrating cells appear in the nervous tissue, many of them polymorphonuclears and others resembling those seen around the vessels. In gray matter of lower portion is a focus of hemorrhage with destruction of nervous tissue and surrounded by a zone of edema with diffuse infiltration of cells.



**Cervical Cord:** The lymph-channels of the pia mater and those surrounding all vessels entering the cord are packed with lymphoid and endothelial cells, especially marked in that portion of the pia located in the anterior fissure, although the perivascular channels of the small branches entering the white matter are uniformly involved, especially those located near the ventral roots. Sections from various levels in this portion of the cord show the gray matter occupied by a hemorrhage, with surrounding zone densely infiltrated by inflammatory cells. In this region the ganglion cells are either degenerated or have disappeared entirely. The infiltration often extends backward into the gray matter of the posterior horn involving Clarke's column. In the denser areas many nuclei are pyknotic and show varying stages of karyorrhexis, the nuclear fragments being

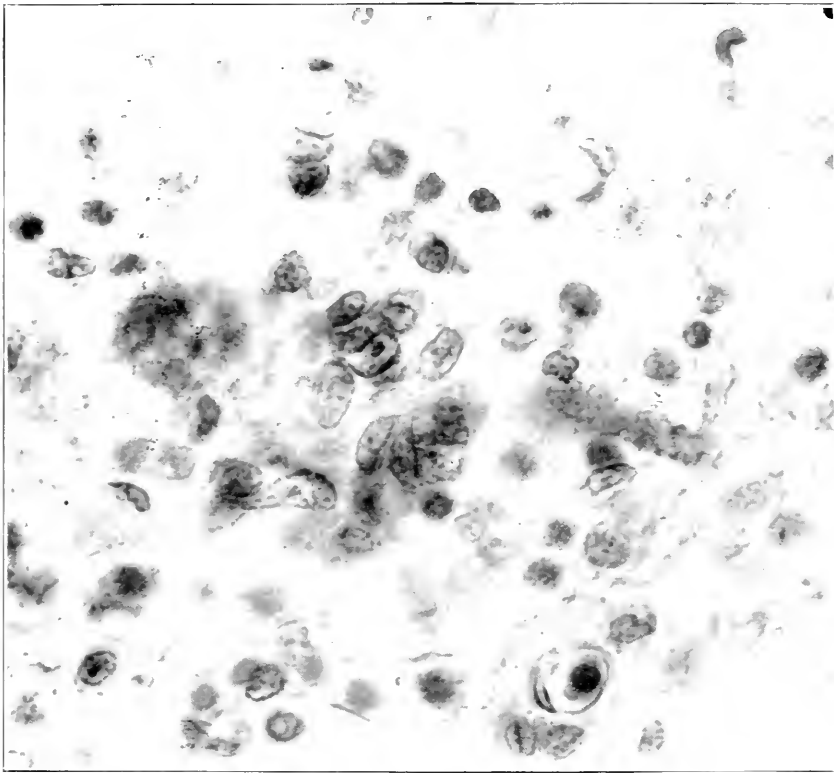


Fig. 16.—Giant-cell enclosing remains of ganglion cell (Case 4).

sometimes taken up by the phagocytic cells. One particularly degenerated ganglion cell is found surrounded by a group of endothelial cells. The gray matter of the opposite side always shows more or less diffuse and focal infiltration, but in many places, often in the region of infiltrated areas, apparently normal ganglion cells may be found. The capillaries in the gray matter are widely distended, but show no evidence of thrombus formation. Occasionally the ventral nerve-roots are edematous and diffusely infiltrated by cells of a lymphoid type. Cross-sections of many of the dilated vessels show an apparent increase in the number of lymphoid cells, suggesting a possible source of origin.

**Thoracic Cord:** Occasional small hemorrhages appear in the anterior horns, but the cellular infiltration, even in the presence of the hemorrhages, is less marked than in the cervical portion.

**Lumbar Cord:** Hemorrhages appear in anterior horns of both sides with excessive destruction of the gray matter and very dense infiltration of cells. There is edema of the white matter extending into the anterior nerve-roots and even involving the posterior columns.

**Sacral Cord:** Free from hemorrhages, but shows both focal and diffuse infiltration of cells in the gray matter and packing of the perivascular spaces. Marchi stain at various levels failed to show definite evidence of degeneration. In sections stained by Gram-Weigert method the presence of micro-organisms could not be demonstrated.

**CASE 2.**—Baby boy, aged 2½. Acute febrile attack with slight diarrhea. On the fifth day developed paralysis of right arm and leg, later involving left arm and leg. Death on eighth day from paralysis of respiratory muscles.

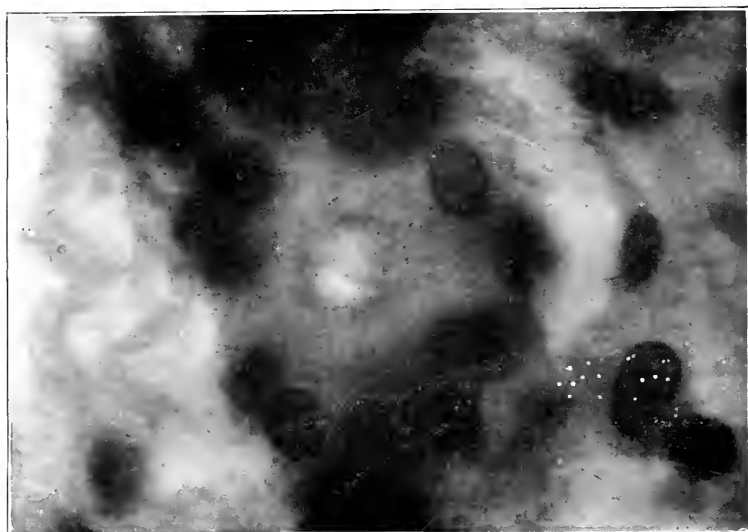


Fig. 17.—Giant-cell formation (Case 14).

**Autopsy.**—July 29, 1909, eleven hours post mortem. Body is that of a normally developed, well-nourished male infant. Body packed in ice and previously embalmed by injection of 2 oz. (?) of fluid in right axillary artery. Section limited to examination of spinal cord. On exposing dura of cord and incising region of cauda, about 30 c.c. of clear fluid escapes. On removing dura with enclosed cord and exposing pia-arachnoid, vessels are deeply congested. Surface clear and free from evidence of exudate. Odor of formaldehyd perceptible. Transverse sections made about 1 cm. apart. In upper portion of cervical enlargement in the anterior horn of the right side is a swollen, softened area showing a small hemorrhagic center. This hemorrhage measures about 3 mm. in length. No other gross hemorrhages observed, but the gray matter of both anterior horns in the cervical and lumbar swellings is softened and has a yellowish tinge.

**Diagnosis.**—Acute hemorrhagic anterior poliomyelitis.

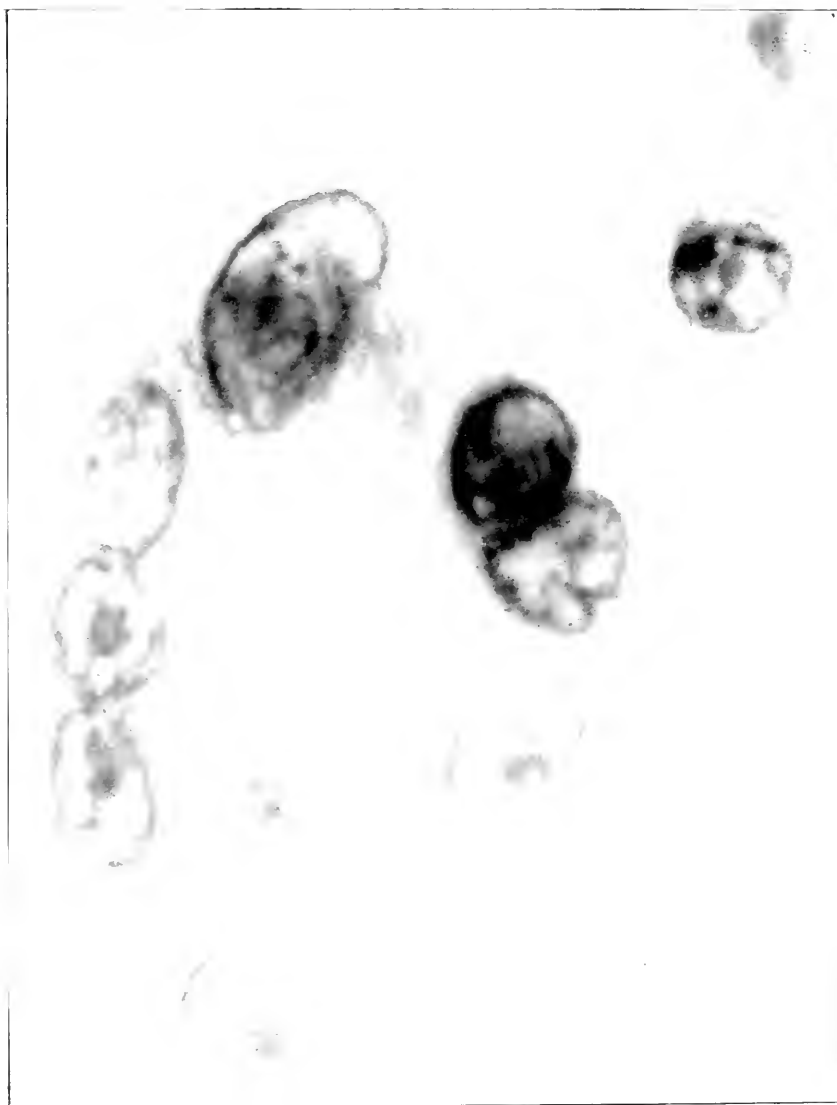


Fig. 18.—Large multinucleated cell (Case 4).

*Histological Examination.*—In sections from the cervical swelling one anterior horn is the seat of several small hemorrhages surrounded by dense masses of inflammatory cells, the endothelial type largely predominating. Many of these cells contain fragments of other cells, while others are swollen and their cytoplasm shows large vacuoles. Sections stained with thionin show many mitotic figures among these large cells, indicating active proliferation. The small capillaries are widely and often irregularly dilated and either closely packed with blood cells or empty, these latter giving the appearance of vessels previously over-distended, suddenly relieved of their contents and unable to return to normal caliber. This phenomenon never appears except in the region of hemorrhages. Ganglion cells in this area are wholly destroyed. The opposite horn is only slightly involved and shows many normal appearing nerve-cells. The pial and perivascular changes resemble those seen in Case 1, except for the diminution in the number of polymorphonuclear leukocytes seen in the exudate. There is no evidence of thrombosis or embolism.

Sections from the thoracic and lumbar portions are free from hemorrhages but the gray matter of the anterior horns shows varying amounts of inflammatory infiltration and destruction of nerve elements, the lesions always being more pronounced on one side than on the other.

In the pial lymph-channels are found small groups of lymphoid and endothelial cells, but in every case these are more numerous and more densely packed in the perivascular channels of the cord substance. The lumbar region is not as markedly involved as the cervical. As in Case 1, the infiltration often extends into the gray matter of the posterior horns and the adventitial sheaths of the vessels of the posterior columns occasionally contain groups of cells.

Gram-Weigert stain for organisms and special stains for demonstrating the presence of Negri or other intracellular bodies in the ganglion cells were negative.

*CASE 3.*—Baby girl, aged 3. Acute attack of high fever, accompanied by aching of lower limbs and pain in back. Motor paralysis of both legs and left arm noticed on third day. On the following day there was complete paralysis of all extremities and beginning involvement of the muscles of respiration. Death on twelfth day.

*Autopsy.*—Oct. 8, 1909, two and one-half hours post mortem. Body is that of a normally developed, well-nourished female infant. The skin of face, neck, trunk and upper portions of limbs is thickly studded with a white miliary papulo-vesicular eruption. (This had followed the injection of a dose of antistreptococcic serum during the illness.) Peritoneal, pleural and pericardial cavities normal. Beneath epicardium are a few petechial hemorrhages along the line of the left coronary artery. Heart muscle shows cloudy swelling. Lungs contain dark congested areas in dependent portions. No evidence of nodules or consolidation. Mucous membrane of bronchi reddened and lumina filled with frothy mucus. Peribronchial lymph-nodes swollen and congested. Spleen normal in size. Pulp congested, soft, and lymph nodules are prominent. Liver is swollen and cloudy. Pancreas and gastro-intestinal tract and adrenals normal. Kidneys swollen, deeply congested and cut surfaces cloudy. Pharynx, tonsils, larynx, trachea, thyroid and thymus free from any evidence of inflammation or disease.

*Head:* On removing calvarium and reflecting dura, the vessels of pia-arachnoid are deeply injected. Careful sectioning of brain, including pons and medulla, fails to reveal gross lesion.

*Cord:* Examination of cord shows deep congestion of vessels. Cerebrospinal fluid is clear and not increased in amount. No evidence of exudate on surface. Sectioned transversely, upper cervical region shows congestion of the anterior horns. In the cervical swelling a softened hemorrhagic area involves the entire left anterior horn. Below the cervical swelling a small hemorrhagic focus appears



Fig. 19.—Giant cells enclosing nerve cell with adjacent foreign body (Case 4).

in the right anterior horn. The thoracic portion, aside from congestion, especially of the gray matter, appears normal for a distance of 6 cm., when a small hemorrhage again appears on the left side. In the lumbar swelling hemorrhages are present on both sides and involve the gray matter of the anterior horns as far as the last sacral segment.

*Diagnoses.*—Acute hemorrhagic anterior poliomyelitis. Congestion of pia-arachnoid of brain and cord. Cloudy swelling of heart, liver and kidneys. Sub-epicardial hemorrhages. Papulo-vesicular cutaneous eruption.

*Histological Examination.*—Sections of the abdominal and thoracic viscera show conditions closely resembling those found in Case 1, the changes in the spleen, lymph nodes, and thymus being fully as prominent as those previously described. Cerebrum and cerebellum free from evidence of lesion except for deep congestion of vessels and the presence of occasional polymorphonuclear leukocytes and lymphoid cells in the tissue spaces of the pia-arachnoid. Cross sections of the blood-vessels of the pia show an apparent increase in the total number of

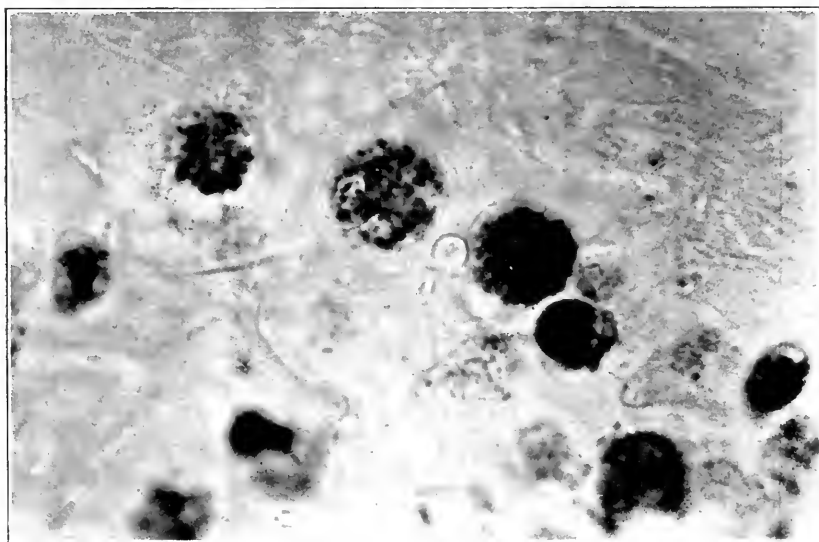


Fig. 20.—Endothelial cells in gray matter containing fat droplets (Case 4), osmic acid stain.

polymorphonuclear leukocytes. Sections of basal ganglia and cerebral peduncles show more intense congestion of vessels and occasional groups of cells in the surrounding lymph-channels of the small branches. This infiltration around the vessels becomes more marked in the upper portion of the medulla, and near the lower portion beneath the ependyma of the fourth ventricle a small hemorrhage appears, with extensive diffuse infiltration of lymphoid and endothelial cells accompanied by edema of nervous tissue.

The ganglion cells in this region are in various stages of degeneration, some being wholly necrotic. The perivascular spaces are packed with cells and near the affected areas the red blood corpuscles are densely massed in the irregularly distended capillaries, so that often, even in very thin sections, they appear fused into a more or less homogeneous mass, resembling a forming thrombus. In pass-

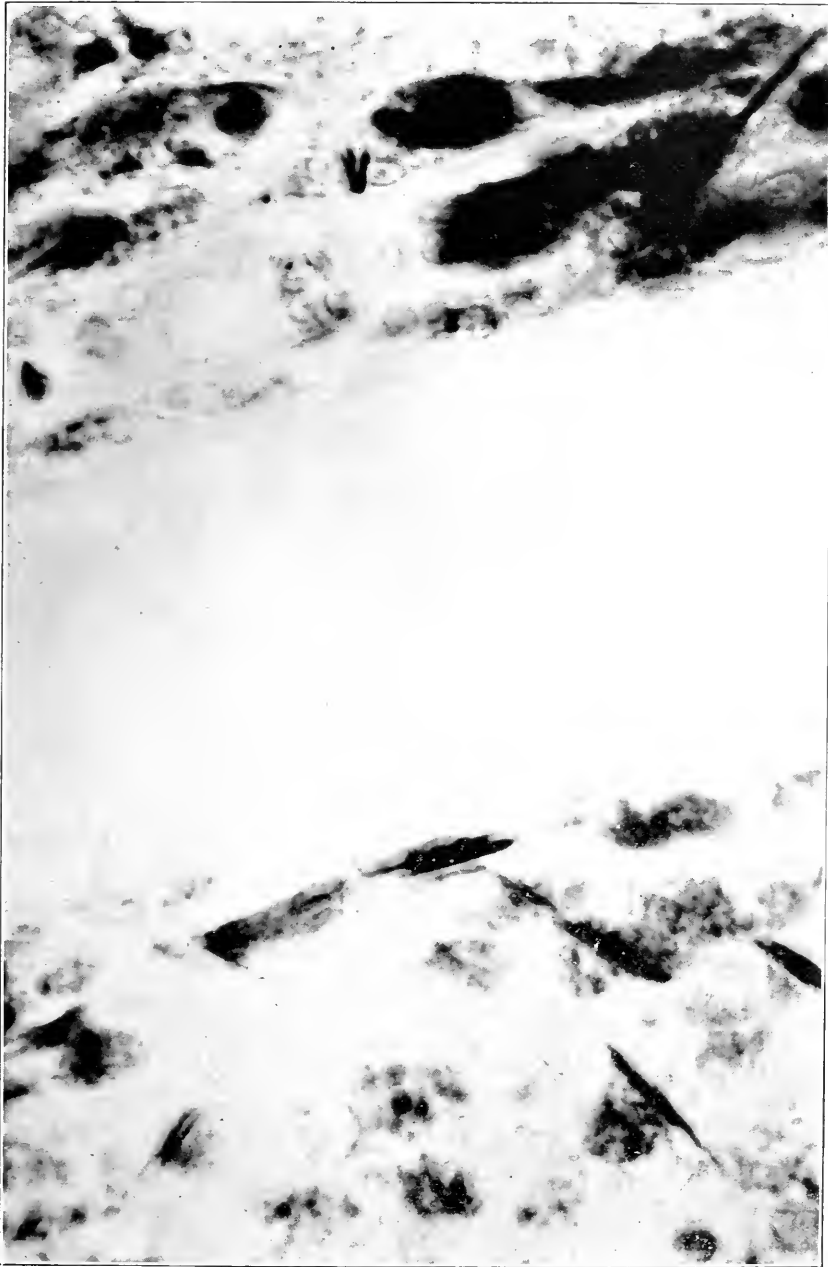


Fig. 21.—Fatty degeneration of cells of blood-vessel walls (Case 4): osmic acid stain.

ing down the cord, sections at various levels show areas of hemorrhage and inflammatory infiltration similar to those observed in Cases 1 and 2, but much more intense in degree. These areas are centered always in the gray matter of the anterior horns, but, as before noted, often invade the posterior portions of the cord. Near the foci of hemorrhage in every instance the dilated capillaries suggest the appearance of complete stasis of the blood-stream. The lymph-channels of the pia mater throughout the entire cord are noticeably less infiltrated than those surrounding the vessels of the cord itself. Cross sections of vessels show increase in the number of polymorphonuclear leukocytes, but very few cells of this type appear in the exudate. Sections of cord with nerve-roots and also of nerves of cauda stained by Marchi method present occasional fibers with beginning degeneration.

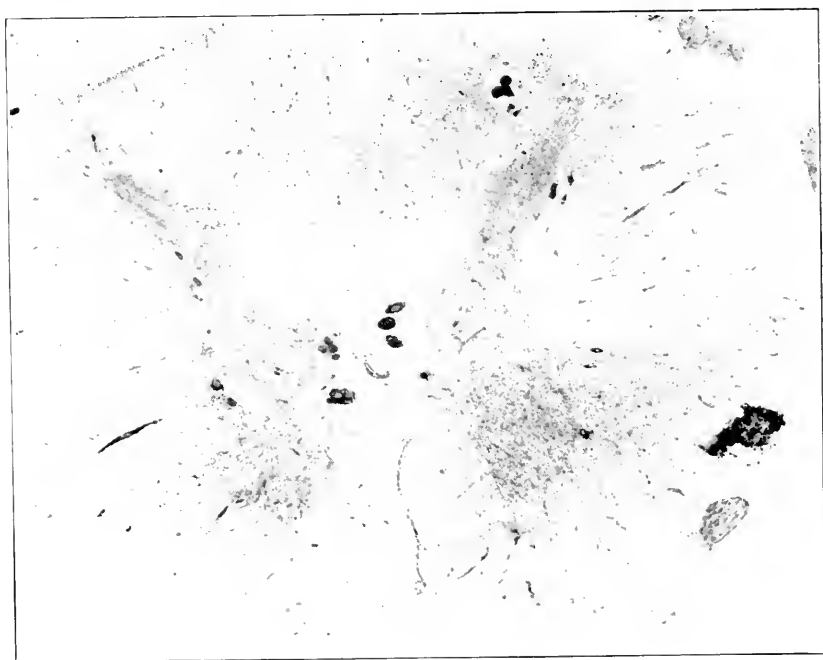


Fig. 22.—Cord (Case 5), showing diffuse infiltration of anterior horns and vessels surrounded by cells.

CASE 1.—A girl, aged 6, suffered typical acute attack in early part of August, 1909, and rapidly developed complete motor paralysis of both lower limbs and partial paralysis of upper limbs, more marked on the left side.<sup>30</sup> October 13 she was admitted to the State Hospital for Crippled and Deformed Children and on October 22 developed an attack of bronchopneumonia. By November 1 she had apparently completely recovered from this. December 25 was seized with an attack of labored breathing; a few hours later showed clear evidences of pneumonia. Death on Jan. 3, 1910, nearly five months after the acute attack.

30. A 2-year-old boy and a month-old baby in this family were taken sick at the same time and died after a few days' illness. The clinical diagnosis was anterior poliomyelitis in both cases; no autopsies obtained.



*Autopsy.*—Jan. 5, 1910, fifty hours post mortem. Body is that of a fairly well-developed, poorly nourished girl. Muscles of both upper and lower extremities show decided atrophy, those of the right arm and forearm being least affected. The lungs show patches of consolidation almost uniformly scattered over all the lobes of both sides. From cut bronchioles purulent fluid escapes on pressure. Peribronchial lymph-nodes soft and swollen. Remaining viscera of trunk, aside from deep congestion and cloudy swelling of liver and kidneys, are apparently normal. Head not examined.

On incising dura of cord, in the lower portion of spinal canal a normal amount of clear serum escapes. On removing cord and making transverse incisions about

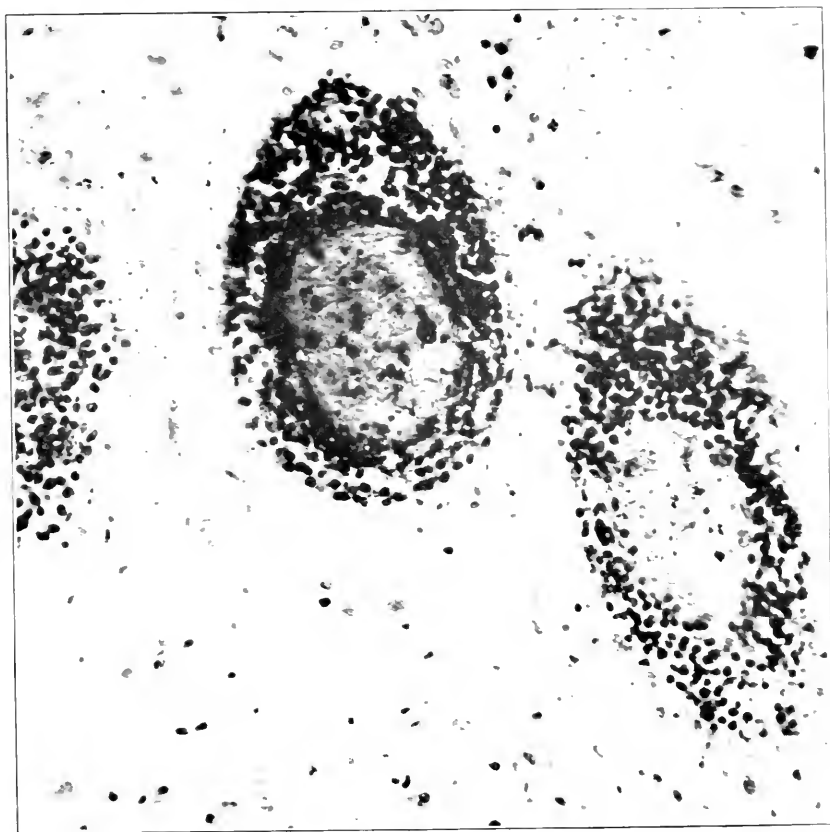


Fig. 23.—Perivascular collections of cells; enlarged photograph of vessels in Figure 22.

1 cm. apart the following lesions appear: In the upper portion of the cervical swelling in the anterior horn of the left side is a softened depressed grayish-red area. This lesion extends through the cervical swelling. About the mid-portion a similar, but smaller area appears on the right side. In the midthoracic portion as far down as the lumbar swelling, minute, reddish, softened areas are seen at intervals in the anterior horns. In the lumbar swelling both anterior

horns are softened and of a grayish and yellowish-red color. The sacral cord is apparently more nearly normal. Portions of mid-brain removed through foramen magnum.

*Diagnoses.*—Acute bronchopneumonia. Anterior poliomyelitis with softening of cord and atrophy of muscles of limbs.

*Histological Examination.*—Heart: Swelling of muscle fibers and edema of interstitial tissue. Lungs: Well developed bronchopneumonia, showing in addition to the usual features marked hyperplasia of the peribronchial lymphoid tissue. Lymph-node (mediastinal): Marked dilation of sinuses which are filled



Fig. 24.—Anterior fissure and pia mater of cord (Case 6): congestion and infiltration.

with lymphoid, polymorphonuclear and proliferated endothelial cells, many of which are phagocytic for other cells and brown pigment granules. Spleen: Sinuses resemble those of lymph node. Centers of Malpighian bodies filled with masses of endothelial-like cells undergoing hyaline fibrinoid changes. Liver and kidneys show congestion, granular degeneration of the pulp-cells, and edema of connective

tissue. Thymus resembles organ in Case 1, except for atrophy of lymphoid elements and increase of fat-bearing connective tissue.

Mid-brain: A section passing through the substantia nigra shows one large vessel with its outer sheath closely packed by lymphoid cells. The characteristically pigmented ganglion cells are in the early stages of degeneration.

Spinal Cord: The location and extent of the lesions at various levels differs very little from those described in the previous cases, but the appearances of these lesions present the following differences: 1. The pial and perivascular infiltration is less dense and composed almost wholly of lymphoid cells. 2. The gray matter of the affected anterior horns shows wide edematous spaces with fewer

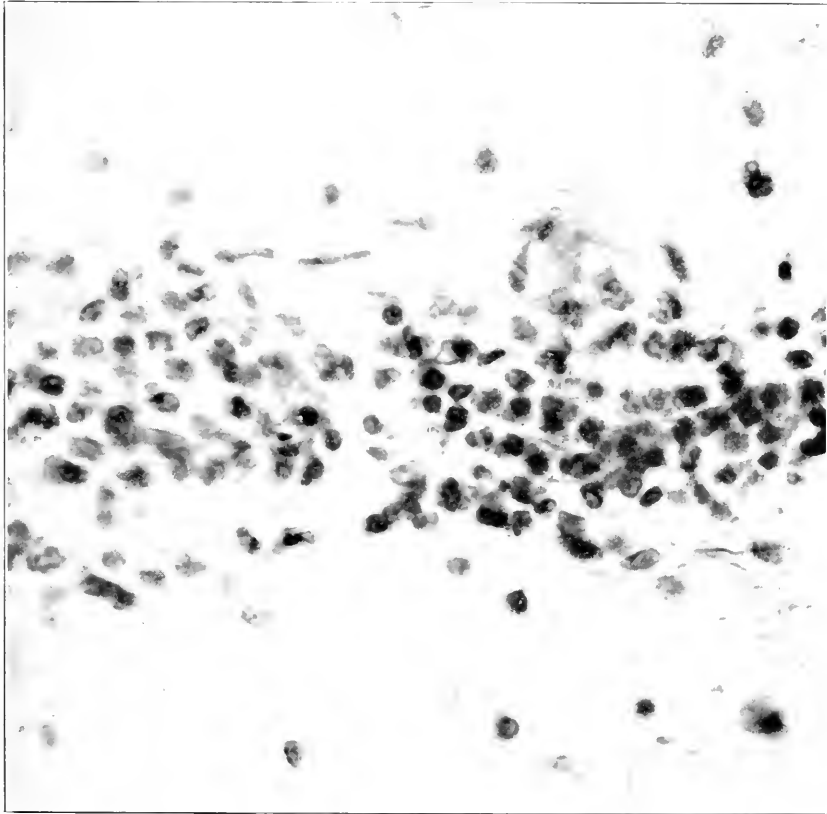


Fig. 25.—Cells in anterior fissure from Figure 24.

cells. 3. These cells are uniformly swollen with small dark-staining nuclei pushed to one side. Staining by the Marchi method demonstrates varying sized fat globules in the cytoplasm. Occasional lymphoid cells appear in the loose meshes. 4. In these areas a few ganglion cells remain. These are shrunken and their cytoplasm often densely packed by small basic-staining granules. Sometimes such a cell is surrounded by a large number of oval vesicular nuclei giving the appearance of a foreign body giant-cell (neuronophage). Small multinucleated cells are fairly common. 5. In these same regions blood-vessels are noticeably

reduced in size and number and widely separated by large edematous spaces. The Marchi stain reveals advanced fatty changes in the walls of these vessels. 6. In portions of the thoracic cord there is shrinking of the gray matter of the affected side, but nowhere is there any evidence of proliferation of neuroglia tissue or vascular repair. 7. Sections of the anterior nerve-roots and bundles of nerves from cauda and sacral plexus show varying degrees of degeneration when stained by the Marchi method.

CASE 5.—Girl, aged 15. Acute attack of chills and fever lasting two days, followed by motor paralysis of lower extremities and rapid involvement of upper extremities except fingers of right hand. On the eleventh day she had a second chill followed by fever and labored breathing. Death occurred on fifteenth day.

*Autopsy*.—Dec. 12, 1909, thirteen hours post mortem. Body is that of a well-developed, poorly nourished young girl. Serous cavities and heart normal. The

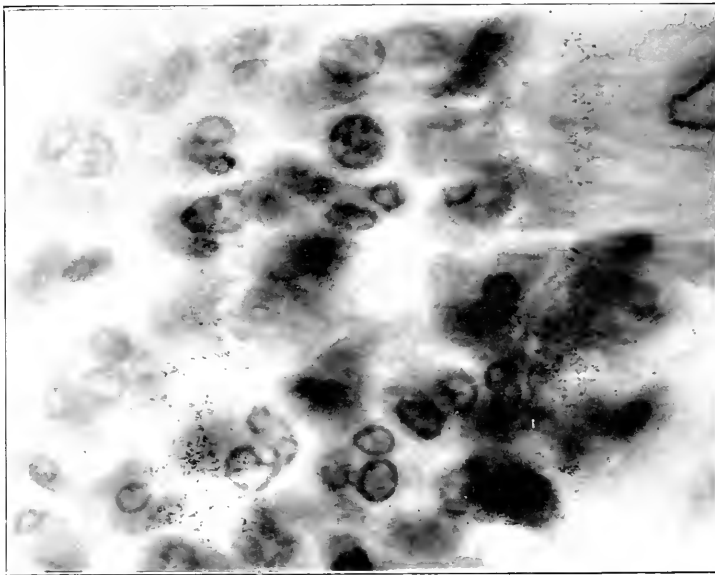


Fig. 26.—Polymorphonuclear leukocytes around vessel from Figure 24.

left lung shows an area in each lobe posteriorly which is dark bluish-red in color, non-crepitant and firm. Cut surface is rather dry and granular. In the dependent portions of right lower lobe are numerous scattered rounded nodules of consolidation. The mucous membrane of the bronchi is injected and the lumina contain frothy mucopurulent fluid. Peribronchial lymph-nodes swollen and congested. One shows a small focus of calcification. Liver, spleen and kidneys apparently normal except for congestion. Thymus atrophied. Brain surface deeply congested. No excess of fluid. Careful section shows no demonstrable lesion in cerebrum, cerebellum, or basal ganglia. On the left side of the medulla is a pin-point hemorrhage located in the gray matter. Middle ears and bony air-spaces normal. Cord shows congested membranes with only a small amount of clear spinal fluid. In the cervical cord the gray matter of the anterior horns is reddened and softened. In the cervical swelling hemorrhages appear on both sides. The thoracic portion is free from hemorrhages, but the gray matter is

soft, congested and swollen. Both anterior horns in the lumbar enlargement show hemorrhages and swelling of the cord.

*Diagnoses.*—Acute hemorrhagic anterior poliomyelitis. Acute terminal bronchopneumonia. Congestion of membranes of cord and brain. Calcification of bronchial lymph-node.

*Histological Examination.*—Lungs: Sections from dependent portions give the typical appearances of bronchopneumonia. Bronchial lymph-node resembles that described in Case 4. Aside from congestion, liver, kidneys and spleen appear normal. Lymphoid tissue of thymus gland reduced in amount and Hassall's corpuscles are very prominent, suggesting the appearances seen in the thymus in Case 1.



Fig. 27.—Monkey inoculated with spinal cord from patient 5; paralysis following brain abscess.

*Medulla:* In the gray matter of one side is a focus of hemorrhage surrounded by a very dense mass of inflammatory cells. In this area the ganglion cells are uniformly necrotic, appearing as swollen eosin-staining homogeneous bodies. In the cells of the exudate karyorrhexis is prominent, evidenced by innumerable basic-staining granules of nuclear chromatin. These granules are often contained in the cytoplasm of the endothelial cells, which are numerous both in this exudate and in that surrounding the blood-vessels. The opposite side shows a slightly

lessened amount of infiltration without hemorrhage, but only an occasional ganglion cell may be found. The blood-vessels are dilated and their contents sometimes simulate the appearance of thrombosis, as in Case 3. Sections from lower levels differ little from those described in Case 1. The absence of polymorphonuclear leukocytes from the exudate is a marked feature. The anterior nerve-roots show a slight lymphoid cell infiltration and their blood-vessels, as well as those of the posterior roots, are widely dilated. In sections of the spinal ganglia opposite the lumbar swelling there is degeneration and swelling of the ganglion cells and edema with lymphoid cell infiltration of the interstitial tissue. Marchi stain demonstrates advanced fatty changes in the nerve fibers.

**CASE 6.**—Boy, aged 17. Taken sick with dull pains in chest and back and general prostration. Two days later had a severe chill followed by high fever accompanied by pain in chest, cough, and vomiting. No history of paralysis could be obtained, but the father stated that shortly before death patient developed difficulty in swallowing.

**Autopsy.**—Oct. 16, 1909, thirty-three hours post mortem. Body is that of a normally developed, poorly nourished boy, showing slight general subcutaneous edema. Mesenteric lymph nodes markedly swollen, especially near the cecum where the largest is bean-shaped and fully 4 cm. in length. Pleural cavities irregularly interrupted by tough fibrous adhesions. Heart shows numerous fine hemorrhages beneath epicardium; muscle soft and cloudy. Lungs show small subpleural hemorrhages. Both lower lobes are thickly studded with small patches and nodules of consolidation. On section of these areas, from cut bronchioles thick yellow pus escapes on pressure. In lingula of left lung are two large wedge-shaped areas of interstitial emphysema. Left apex shows a firm fibrous nodule containing a focus of calcification. Lymph-nodes at bifurcation of trachea contain caseous centers with calcareous capsules. Spleen swollen and soft. Pulp scrapes easily and lymph nodules are prominent. Peyer's patches and solitary follicles in ileum are raised, swollen and deeply congested. Kidneys large, pale and soft. Cut surfaces cloudy. Urine removed post mortem shows large amount of albumin and various forms of casts. Aorta presents numerous fine yellowish streaks of atheroma. Trachea congested but shows no evidence of membrane formation. Mucous membrane of throat dark and swollen. Tonsils swollen. No evidence of diphtheria. Head not examined. Cord shows congestion of membranes. Cerebrospinal fluid clear and not excessive in amount. Serial transverse sections of cord show no gross evidence of lesion beyond a slight reddening of gray matter of anterior horns.

**Diagnoses.**—Acute bronchopneumonia. Acute diffuse nephritis. General lymphoid hyperplasia. Old healed pulmonary tuberculosis. Old healed pleuritis.

**Histological Examination.**—Heart: Muscle cells swollen and striations indistinct. Lung: Typical patches of bronchopneumonia with peribronchial lymphoid hyperplasia. Lymph nodes (bronchial and mesenteric): Extreme congestion; otherwise resemble those of Case 4. Spleen: Congestion marked. Centers of lymph-nodules packed with endothelial cells. Intestines: Lymphoid structures are hyperplastic and central portions of follicles and sinuses resemble those of spleen and lymph nodes. Liver: Extreme congestion, especially in central zones of lobules. Granular and vacuolar changes in pulp-cells. Adrenal: Congestion of considerable duration evidenced by atrophy of cell cords of inner zone. Kidney: Acute diffuse nephritis of the tubular type, such as often found in acute toxic fevers of bacterial origin.

**Cord:** Sections at various levels free from any evidence of hemorrhages. In the lymph-spaces of the pia, especially that portion located in the anterior fissure, there is abundant exudate of cells which are largely of the polymorphonuclear

type. A few lymphoid and endothelial cells appear, many of the latter showing phagocytosis. The perivascular spaces in the anterior portions of the cord are closely packed with a similar exudate, and in the gray matter are numerous foci of cells composed chiefly of polymorphonuclear leukocytes. Some of the ganglion cells in these regions are in various stages of degeneration, but they are not apparently diminished in number and many normal appearing cells may be seen. No large or even small areas of gross destruction of gray matter, such as described in the other cases, can be found. The vessels are congested, but show no evidence of thrombosis or even advanced stasis. The cervical and lumbar swellings are most markedly affected and one anterior horn is always more involved than the other. The posterior horns and columns are uniformly unaffected.

#### SUMMARY

Cases 1, 2 and 3 represent the ordinary type of acute lesion with hemorrhages. Cases 4, 5 and 6 are complicated by pneumonia. In Case 4 the patient probably would have died eventually; the pneumonia being only a terminal affair. Case 5 was an institutional case, and the patient, though safely through the acute stages, succumbed to intercurrent infection. Case 6 was so complicated by the occurrence of pneumonia and acute diffuse nephritis that we are inclined to believe the attack of poliomyelitis was only a minor event; and pathologically the lesion certainly is less severe, or more early, than that presented by any of the other cases.

The process as a whole follows a definite and specific course. Whatever may be finally shown to be the agent of infection its "optimum locus" is in the perivascular lymph-channels of the anterior portions of the cord, especially those located in the gray matter. From this site the reaction spreads on the one hand, to the surrounding tissue spaces of the gray matter and, on the other, to the lymph-channels of the white matter and pia, often involving the posterior portions of the cord. We are inclined to believe these channels also represent the avenue of infection, whether it starts from the nasal or some other external surface.

The cells collecting in these spaces are not those to be expected from an ordinary pyogenic infection. Very early in the disease polymorphonuclears appear in small numbers, but they are soon replaced by endothelial cells and lymphocytes, the latter predominating by the end of the second week. The small number of the polymorphonuclear leukocytes in the exudate of all but one of the cases was a noticeable feature. The cellular reaction alone somewhat resembles that seen in the primary and secondary lesions of syphilis. The lymphocytes apparently come from the blood and lymph-streams combined. In cross-sections of dilated vessels their number is often increased and at one point in a vessel-wall active migration of these cells was observed. The endothelial cells arise, we believe, from proliferation of those normally lining the lymph-channels and

spaces. In several areas they showed mitotic figures. They are phagocytic for whole cells and disrupted portions of cells and in turn undergo fatty degeneration of cytoplasm and disintegration. They appear in especially large numbers in the diffuse exudate in the anterior gray matter.

The toxic action of the disease is directed chiefly against the anterior horns. The first noticeable change in addition to the congestion and perivascular collection of cells is edema in the interstitial spaces. This is rapidly followed by focal or diffuse infiltration of cells with or without hemorrhages and accompanied by destruction of both the neuroglia and ganglion cells. Many of these latter, however, persist and sometimes appear normal even in the region of extensive infiltration. They may show various stages of degeneration from irregular grouping and peripheral arrangement of Nissl's granules to edema of cells, loss of nucleus and complete disintegration. In the most prolonged case of this series (Case 5), nerve-cells were found with shrunken outlines and cytoplasm crowded with large basic-staining granules. One of these cells was surrounded by a large number of oval vesicular nuclei, suggesting a giant-cell or so-called neuronophagocytosis. In the later stages the hemorrhage is absorbed, the cells of the exudate disintegrate and proliferation of neuroglia begins the process of repair. The blood-vessels are always congested, especially the capillaries and veins. The Marchi stain demonstrates fatty degeneration in their walls and this factor probably accounts for the loss of elasticity, irregular dilatation and final rupture. We could not satisfy ourselves of the presence of thrombosis in any of our cases. The question does not seem an important one. Granted that the vessel-walls are diseased and overdistended and that the blood-current is so obstructed that it approaches a condition of stasis, then hemorrhages may occur, whether actual thrombus formation is or is not present. These hemorrhages are the most important factor in producing extensive destruction, occurring as they do almost uniformly in the gray matter of the anterior horns. More than any other one lesion they probably tend to bring about a fatal result.

Staining by the Marchi method demonstrates patchy degeneration of nerves in both anterior roots and peripheral nerve fibers. This occurs fairly early in the disease. Special stains for micro-organisms, such as Gram-Weigert, eosin and methylene blue and thionin, were uniformly negative.

Why the process spends itself on the anterior horns has always been a question for active discussion. Undoubtedly the blood-supply is especially abundant through the anterior spinal arteries, but abundant blood-



supply in other portions of the body is not usually considered the most important determining factor for the location of disease processes. That the lesion is specific and definitely selective seems by far the most reasonable supposition and one that conforms with numerous analogies in both the cord and other portions of the body, such as *tabes dorsalis*, typhoid fever, etc.

The location of the lesions has been described under each case. The medulla and cervical and lumbar swellings were most often the seat of hemorrhages, indicating that at these points the selective action of the virus was most manifest. We were not able to find evidence of involvement of the cerebrum or cerebellum, but in two cases the cerebral peduncles and in one instance the basal nuclei showed vessels surrounded by collections of cells.

One noticeable feature not sufficiently emphasized in the literature is the evidence of a general toxemia. The parenchyma of the heart, liver and kidneys was the seat of cloudy swelling and invariably the lymph nodes and spleen showed the customary reaction to the presence of a toxin in the general circulation. Hyperplasia of lymphoid tissue with proliferated and often phagocytic endothelial cells collecting in the sinuses and central portions of the follicles was constantly observed.

Through the kindness of Drs. Flexner and Lewis, we were able to compare the lesions found in our cases with those obtained in the spinal cords of monkeys experimentally inoculated with the poliomyelitis virus. Perivascular collections of cells, diffuse infiltration and hemorrhages in the anterior gray matter were present in various stages. While the structure of the monkey's cord differs somewhat from the human, the lesions seem in every way analogous to those found in our cases.

#### CONCLUSIONS

1. Acute anterior poliomyelitis is a specific infectious disease characterized pathologically by general toxemia affecting the parenchyma of the heart, liver and kidneys and the lymphoid tissues of the body, but spending itself locally on the structures of the spinal cord.

2. Grossly the cord is congested and on transverse section shows softening and often hemorrhages in the gray matter of the anterior horns.

3. In the cord the infectious agent is located in the perivascular lymph-channels of the anterior portions, especially invading the gray matter, but extending to the white matter and pia and occasionally the posterior horns. The brain stem and basal ganglia may be involved. In the cord the medulla and cervical and lumbar swellings are particularly affected.

4. The characteristic lesion consists of collections of cells in the perivascular and pial lymph-channels and tissue spaces of the anterior horns. Of these cells the polymorphonuclear leukocytes appear early and are relatively few in number. They are soon displaced by endothelial cells arising from proliferation of the lining endothelium and lymphocytes coming from the blood and lymph-streams.

5. Edema of the interstitial tissue and degeneration and destruction of the ganglion cells are always present.

6. The vessels are congested, their walls degenerated, and the capillary branches in the gray matter irregularly distended and often ruptured, giving hemorrhages, which always intensify markedly the amount of destruction. Thrombosis was not observed.

7. Early degeneration of nerve fibers from the anterior roots is a constant feature.

8. Stains for micro-organisms were uniformly negative.

## II. BACTERIOLOGY.

BY A. J. CHESLEY, M.D.

To attain our present conception of poliomyelitis the symptomatology and pathology have been broadened to include many variations in symptoms and lesions. To determine the cause of poliomyelitis the etiology has been narrowed to exclude many factors once classified as exciting or causing the disease. All the common diseases, most of the accidents and tribulations incident to childhood have been so classified. Having no evidence of hereditary transmission, and being unable to accept the maternal impression theory, conservative writers advanced a theory that the disease might be due to infection with a specific micro-organism.

A review of the literature shows a remarkable variety and inconsistency in the bacteriological findings of spinal fluids and autopsy materials. At best, only temporary credence has been given to the theory of any micro-organism as the probable cause of the disease. For example the following list is given, which includes a sufficient number of the infectious agents mentioned as probable causes: the staphylococcus (all varieties), the streptococcus, meningococcus, pneumococcus, *Micrococcus catarrhalis*; the bacillus of diphtheria, of anthrax, of influenza, of typhoid, the colon bacillus, the malarial parasite; the virus of rabies, of smallpox, of measles, of scarlet fever, of syphilis, and of whooping-cough.

A Gram-positive coccus, now generally known as Geirsvold's diplococcus (in appreciation of Geirsvold's important work during the Scandinavian epidemic) has received the most attention. Geirsvold's etiological theory, expressed in very conservative terms, brought this coccus into

serious consideration. It has been found in purity in many specimens of spinal fluid withdrawn during life, and in the organs of several patients after death. It has produced symptoms closely resembling those of human poliomyelitis in a few of the animals experimentally infected. It has been recovered in purity from the spinal fluid and tissues of such animals. Some of this work has been done with great care to eliminate the possibility of contamination, and control experiments have practically excluded this possibility. The crucial test is the search for the specific lesions of poliomyelitis. When lesions have been present in the spinal cords of rabbits, guinea-pigs, mice, rats, pigeons or monkeys inoculated with living cultures, or spinal fluid from which pure cultures of Geirsvold's diplococcus were obtained, they have not been the specific lesions of poliomyelitis. By isolation from mixed cultures this coccus has been obtained from eyes, noses and throats of tonsillitis, diphtheria and poliomyelitis patients and from the nose of a nurse caring for a child with poliomyelitis.

During the Pennsylvania epidemic, Drs. Fox and Rucker did some excellent bacteriological work, which is given in detail in the Annual Report of the Commissioner of Health of Pennsylvania for 1907. Their description of the cultural and morphological characteristics of Geirsvold's diplococcus is very complete and coincides exactly with our findings. Other references are purposely omitted, since the recent investigation at the Rockefeller Institute has surpassed all others in value and is a matter of current report.

In Minnesota, free examination of spinal fluid is part of the routine work of the Laboratory Division of the State Board of Health and specimens from twenty cases of poliomyelitis were examined during the epidemic of 1909. The results of this work are valuable as negative evidence, and some of the data relating to motor disturbances in inoculated animals and Geirsvold's diplococcus are as follows:

#### DATA OF SPINAL FLUID EXAMINATION

Spinal fluids from seven patients (five recovered; two died; no autopsies) showed bacteria obviously due to contamination. Several of the animals inoculated with these fluids died, but symptoms and lesions of poliomyelitis were absent. The other animals were well eight months after inoculation.

Spinal fluids from five patients (all died; no autopsies) were perfectly clear. The smears showed only a few lymphocytes. No organisms were found. A rabbit inoculated in the ear vein with 1 c.c. of one fluid remained well and gained 685 gm. in eight months. He was then killed and no lesions were found.

Geirsvold's diplococcus was found in purity in the spinal fluids from seven patients (two died; see Dr. Robertson's Cases 1 and 3; five recovered), and also in cultures from the blood, mouth, lung, spleen, kidney, middle ear and brain substance of the patient in Case 3.

TESTS TO DETERMINE THE PATHOGENIC RELATION OF GEIRSVOLD'S  
DIPLOCOCCUS

Cultures from two of the patients recovering with paralysis, and from the two patients just noted who died, were grown for forty-eight hours on plain agar slants.

Eight rabbits of about the same size and weight were selected for inoculation. Sterile physiological salt solution was added to each slant and the cultures rubbed up to give uniform milky emulsions.

Each rabbit received 0.3 c.c. of a single emulsion. Each culture was injected into two rabbits, one rabbit being intravenously and the other subdurally infected.

One of the cultures killed both rabbits. The one inoculated in the ear vein died from acute pneumonia; the one inoculated subdurally died from meningitis, and, although the diplococcus was recovered in purity from his brain, no lesions of poliomyelitis were present in either case. The other six rabbits were not in the least affected by the inoculations.

It will suffice to state that twenty-eight rabbits, six guinea-pigs, two white mice and two rats were inoculated and, in spite of some symptoms of motor disturbances (amounting to complete paralysis in one animal), no specific lesions of poliomyelitis were discovered in sections of spinal cords. The spinal fluid of a rabbit dead of meningitis, caused by subdural injection of Geirsvold's diplococcus obtained from Case 3, was put into the brain of another rabbit. This rabbit developed a paralysis of the hind legs which progressed until he died on the forty-fourth day after inoculation from paralysis of respiration. He was greatly emaciated, his tendon reflexes were absent, and no response could be obtained by electric stimuli during the two days preceding death. The bacteriological and pathological findings were negative for the diplococcus and for lesions of poliomyelitis.

This case is cited to show how easily one might be led to misinterpret symptoms in an inoculated animal, if the pathology of the case is not worked out carefully.

Our experimental work confirms the opinion previously expressed by other observers, that Geirsvold's diplococcus is not a causative factor in poliomyelitis.

In the meanwhile the production of experimental poliomyelitis in monkeys had been reported by Drs. Flexner and Lewis of the Rockefeller Institute. We secured from a kindly disposed owner of a near-by zoological garden two monkeys (*Macacus rhesus*) which had become acclimated to the cold Minnesota winter, and waited for another autopsy to give us some material for experimentation. The next post-mortem examination was Case 5 (see Dr. Robertson's notes) and it gave in cultures from the spinal fluid a mixture containing pneumococci. A terminal pneumonia readily accounted for the presence of this organism. Since a culture from the substance of the cord showed no growth after forty-eight hours incubation, the female monkey was chloroformed and 0.5 c.c. of a thick emulsion of spinal cord from patient 5 was injected into the brain substance on the right side. She had no trouble from the operation or the wound, which healed without suppuration in a few days. Not until the sixth day did she show any change in playfulness or appetite. For three days thereafter her appetite was impaired and her left foot and leg were not as warm as the other one. Then some paresis developed, chiefly of the flexor groups of the left arm and leg. She was very sick for three days, although her temperature and leukocyte count did not fluctuate.

tuates much more than before she was inoculated. The severity of her general illness lessened, but the paralysis remained. Some loss of weight occurred and wasting of the flexor groups of muscles in the affected limbs became apparent. She was photographed on the twenty-second day after inoculation and then chloroformed, since she seemed to be suffering. A complete autopsy showed no macroscopic lesion in any organ except the brain. Here a large abscess took up about half the right hemisphere and from it the pneumococcus was obtained in purity. Microscopic examination of all organs proved the absence of lesions of poliomyelitis.

This sudden onset of a selective paralysis following a short period of general malaise might have been mistaken for acute anterior poliomyelitis had symptoms alone been considered. This emphasizes the previous assertion that symptoms in inoculated animals must be supported by pathological findings to have any value as experimental evidence.

The safety and utility of lumbar puncture as an aid in diagnosis and treatment should be borne in mind and the examination of spinal fluid should be a routine measure in public health laboratories.

We look forward confidently to the solution of this etiological problem in the near future and wish the workers of the Rockefeller Institute victory over acute anterior poliomyelitis equal to their success in epidemic cerebrospinal meningitis.

## PHAGOCYTOSIS OF RED BLOOD-CELLS AFTER TRANSFUSION \*

J. GARDNER HOPKINS, M.D.  
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A patient suffering from an extreme anemia, resembling the primary pernicious type, was admitted to St. Luke's Hospital on the service of Dr. Theodore C. Janeway. Immediately following transfusion, smears of the peripheral blood showed great numbers of polymorphonuclear neutrophil leukocytes containing red blood cells. The picture was so unique and so suggestive as to certain results of transfusion that it seemed worth reporting.

### REPORT OF CASE

*Abstract of History.*—The patient was a man of 48, who for eight years had lived in Porto Rico. His health was excellent up to about eight months before his admission, from which time he dated his illness. At first he lost appetite, began to be drowsy and easily fatigued, and lost weight. Later he had diarrhea, passing mucus but no blood. This had recurred at intervals up to the time he was seen. He had had one period of improvement, but for a month previous to admission he had grown steadily and rapidly worse. He had lost over 35 pounds, more than one-quarter his weight.

*Examination.*—When admitted he was extremely emaciated. His skin was pale, but not lemon yellow. The physical examination was practically negative. The stools were brown and fluid and contained no blood. After long search three actively motile amebas were found, but no eggs of parasites. The urine contained a faint trace of albumin and a few hyaline casts; otherwise it was normal. The pulse was from 80 to 110; temperature 98 to 99.8 F.; respirations 24. The blood contained 1,350,000 red cells, and 4,000 leukocytes to the c. mm. Hemoglobin 23 per cent.; (Fleischl-Miescher). Color index 0.85. Polymorphonuclears, 49 per cent.; lymphocytes, 48 per cent.; eosinophils, 3 per cent. The red cells varied greatly, some 3 to 4 microns, some 10 to 14 microns in diameter; the majority were large, 8 to 9 microns. There were many poikilocytes, considerable polychromatophilia and a few normoblasts were found. The diagnosis lay between a chronic amebic dysentery with extreme secondary anemia and primary pernicious anemia of an irregular type.

*Course of Disease.*—After admission the patient continued to grow worse. In five days his red cells fell to 850,000, his hemoglobin to 18 per cent., the leukocytes to 2,800, with 56 per cent. of lymphocytes. On the tenth day his red cell count was 700,000, his hemoglobin 14 per cent. His condition was so serious that it was decided to try transfusion. His brother volunteered as a donor, and his serum and the patient's serum were tested by Dr. Hans Zinsser for isohemolysins and agglutinins. The patient's undiluted serum agglutinated the donor's corpuscles markedly, and after standing twelve hours in the ice-box there was

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\* From the Pathological Department of St. Luke's Hospital, New York.

slight hemolysis. Four other normal individuals were tested, none of whose serums agglutinated or hemolyzed the patient's corpuscles. In combination with the patient's undiluted serum (equal parts of corpuscle emulsion and serum), one volunteer's corpuscles were fairly well agglutinated, another's slightly agglutinated, and those from the other two not at all. There was no hemolysis in any of the tubes on standing in the cold. As it has been suggested that serums may agglutinate when diluted, which do not agglutinate in concentration, dilutions of the patient's serum with 0.85 per cent. salt solution from 1 in 2 to 1 in 10 were tested, but showed no agglutination with cells from any of the four sources. Unfortunately, the two volunteers whose corpuscles showed no agglutination withdrew, and the one whose cells were slightly agglutinated had to be made the donor.

*Transfusion.*—This was performed by Dr. H. H. M. Lyle. A free flow was established from the donor's radial artery to the median basilic vein of the patient, and allowed to continue for one-half hour. After the operation the patient had



Fig. 1.—Megaloblast from blood after operation. (Wood stain;  $\times$  1,000.)

incontinence of feces, and was very restless and somewhat irrational. He bled from the transfusion wound and from a needle puncture in his finger, but the bleeding was soon controlled. About six hours after the operation he became comatose, developed a hemiplegia and died three hours later.

#### AUTOPSY FINDINGS

*Bone-Marrow.*—This was obtained from three or four inches of the middle of the shaft of the humerus and femur only. It was fatty in consistence and of a diffuse pink color, with small dark red dots. Sections showed fatty tissue with minute hemorrhages, and small islands of cellular marrow in which myelocytes of various types predominated over the red cells. There were few normoblasts and still fewer megaloblasts. Phagocytic cells containing from two to six red cells

were numerous, but these were all of endothelial type with small oval vesicular nucleus. Some polynuclear cells showed yellowish particles, but none were found with distinct red cell inclusions.

*Spleen*.—This was slightly enlarged, soft and congested. Microscopically, the sinuses were dilated with blood and the pulp packed with red cells. An occasional mononuclear phagocyte containing red cells was found in the sinuses. There were scattered granules of hemosiderin both free and in the endothelial cells and polymorphonuclear leucocytes.

*Mesenteric Lymph-Nodes*.—These were enlarged. Microscopically, the sinuses were much dilated. In them were numbers of phagocytes containing red cells, most of which were small and pale. Some of these phagocytes were mononuclear; others were polymorphonuclear.

*Liver*.—This was slightly congested. It showed some fatty degeneration and deposits of hemosiderin, most of which was contained in the endothelial cells. The

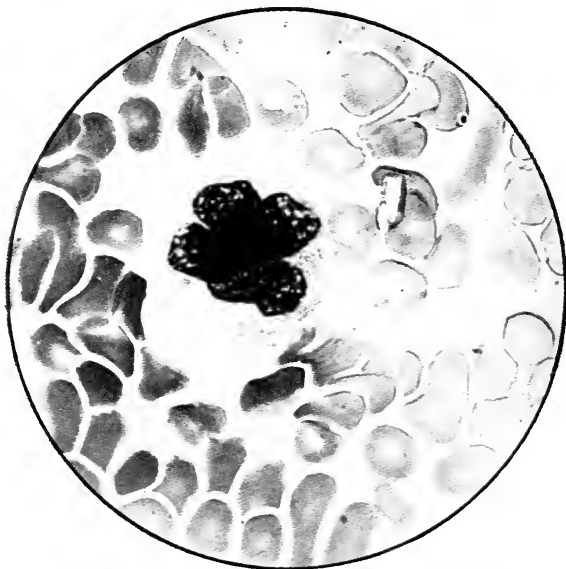


Fig. 2. —Megakaryocyte from blood after operation. (Wood stain;  $\times 1,000$ .)

gastro-intestinal tract was negative except for a few petechiae and some hyperplasia of the solitary lymph follicles. There were no ulcers in the colon and no parasites were found.

#### BLOOD PICTURE AFTER TRANSFUSION

The interesting feature of the case was the blood picture after transfusion. The red cells of the recipient rose from 720,000 per c.mm., with 15 per cent. hemoglobin, to 1,700,000 with 35 per cent. hemoglobin, after the operation. The donor's count fell from 5,000,000 to 3,950,000, and his hemoglobin from 95 per cent. to 75 per cent. Smears of the patient's blood before operation showed no change from previous examinations, but in smears taken immediately afterward, there were found great numbers of phagocytes containing from one to six or more red cells. There was apparently an increase in the number of leukocytes, and a



showed of normoblasts and megaloblasts. About 40 per cent. were small, normal-looking lymphocytes, but there were also some very large lymphocytes and cells with a large nucleus and an abundant deeply basophilic protoplasm resembling Türk's stimulation forms. Most of the polymorphonuclear leukocytes were normal in appearance, but there were some small forms. There were also a number of very large cells measuring 15 to 22 microns, which stained poorly and resembled the large degenerated forms often found in leukocytosis, except that they were much larger. There were a few pale giant cells, one measuring 22 by 27 microns in diameter, with a nucleus composed of five or six round lobes grouped closely together—evidently a megakaryocyte from the marrow. The phagocytic cells all showed neutrophilic granulation, except those that contained so many

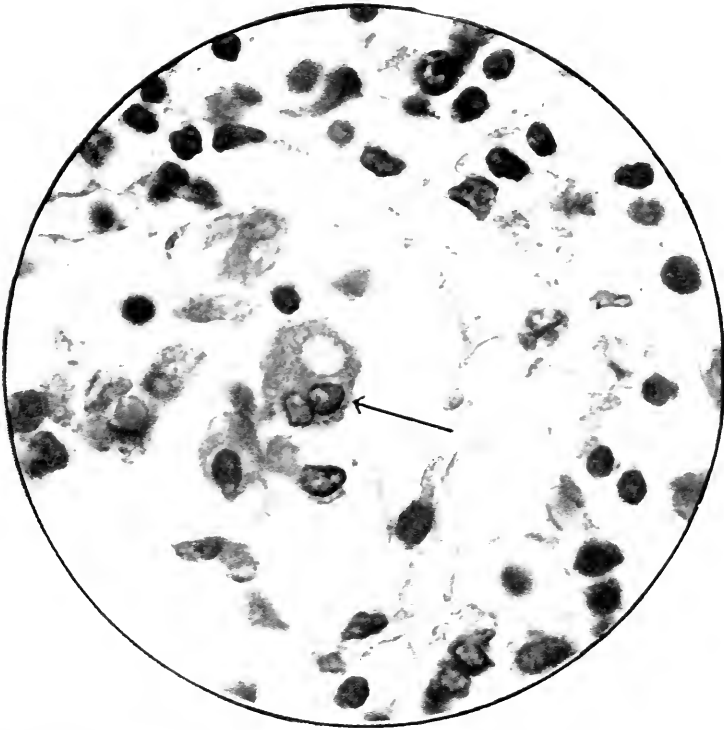


Fig. 3.—Polynuclear phagocyte in sinus of mesenteric lymph-node. (Hematoxylin-eosin;  $\times 1,000$ .)

red cells that the protoplasm was entirely concealed. Some of these contained a mass of red cells packed so closely together that they could not be counted definitely. The smaller ones had a polymorphous nucleus, which, however, took the Jenner stain very faintly; in others the nucleus was compressed into clinks between red cells. Most of the phagocytes were rather large, from 15 to 20 microns in diameter. The ingested red cells were for the most part round and about 6 microns in diameter. A few were irregular and showed processes projecting into the pseudopods of the captor. They stained evenly, but most of them were pale. All gradations were found, from red cells of normal size to colorless

vacuoles of about the same size. Many of the phagocytic leukocytes and others which contained no red cells contained smaller vacuoles.

A differential count of five hundred cells (Jenner stain) gave the following result:

Polymorphonuclear neutrophils .....	54	per cent.
Lymphocytes .....	43	per cent.
Large mononuclears and transitionals.....	1.4	per cent.
Eosinophils .....	0.2	per cent.
Myelocytes .....	1	per cent.
Unclassified .....	0.4	per cent.

Twenty-eight of the polymorphonuclears contained one red cell, and sixteen two or more. In making the count twenty-nine normoblasts and five megaloblasts were seen.

Smears taken after death, which occurred nine hours later, showed no phagocytosis, but normoblasts and megaloblasts were still present in considerable numbers. Many of the leukocytes contained vacuoles which resembled those seen in the postoperative smears.

DIAGNOSIS

The diagnosis was not very certain even post mortem. The case was probably a pernicious anemia in which the complicating diarrhea and rapidly fatal

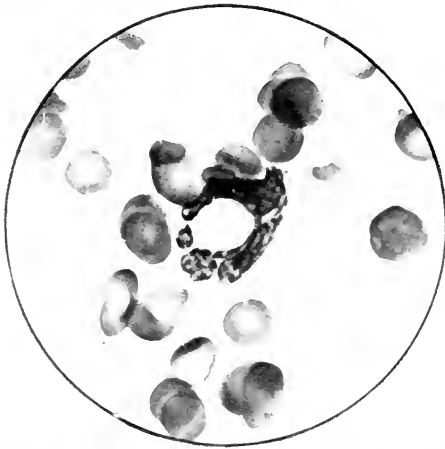


Fig. 4.—Phagocyte with one red cell, showing polymorphous nucleus. (Wood stain;  $\times 1,000$ .)

course prevented the development of the typical bone-marrow picture. The autopsy excluded any parasitic basis for the anemia and the amebas observed must have been *Entamoeba coli*. The size of the red cells and final appearance of typical megaloblasts as well as the pigment deposits in the liver and spleen pointed toward pernicious anemia. There must have been megaloblastic marrow in some of the bones to give origin to these cells, and, moreover, even in typical cases of pernicious anemia, the bone marrow may not show hyperplasia throughout its entire extent. The numerous erythroblasts of course exclude the diagnosis of aplastic anemia.

The only other observations of phagocytosis of red cells in the peripheral blood of man, which I have been able to find in the literature, were

those reported by Rowley,<sup>1</sup> Bartlett,<sup>2</sup> and Van Nys,<sup>3</sup> in 1907. They described two remarkable cases of fatal anemia which resembled each other strikingly. In these cases the blood contained numerous large phagocytes, varying from cells resembling lymphocytes to large mononuclear cells, which ingested every variety of normal elements in the blood. In one of these cases the polymorphonuclear cells were also phagocytic and the serum had the power to cause phagocytosis by the large mononuclear cells of normal blood on the warm stage. The white cell counts were very high, 95,000 to 800,000, which would suggest some relation to leukemia. These cases seem to have very little in common with the one just described.

#### THE MEANING OF THE BLOOD-PICTURE

I am unable to determine the meaning of the blood-picture in this case. The shape, size, and staining properties of the ingested red cells

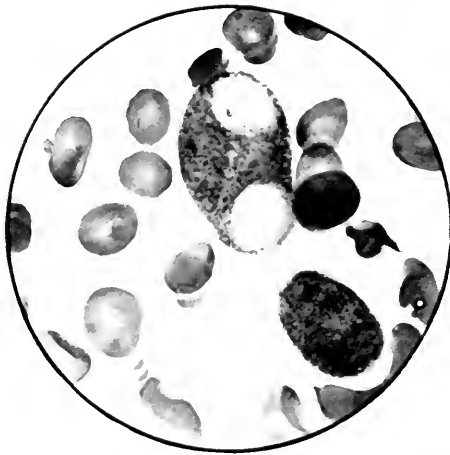


Fig. 5.—Phagocyte with two red cells showing neutrophil granulation. (Jenner stain;  $\times 1,000$ .)

make it seem probable that many of them were from the donor; while the fact that the phagocytes were so numerous and that many of them were atypical, makes it certain that some at least were from the recipient; so that what was observed was probably a phagocytosis of the transfused red cells by the phagocytes of the recipient. This might be explained in two ways: as a washing out into the peripheral blood of phagocytes from

1. Rowley: *Jour. Exper. Med.*, 1908, x, 78.

2. Bartlett: *Boston Med. and Surg. Jour.*, 1907, clvi, 629.

3. Van Nys: *Boston Med. and Surg. Jour.*, 1907, clvi, 390.

the blood-destroying organs, or as a phagocytosis due to the presence of an hemopsonin in one of the serums.

In regard to the first possibility, there is ample evidence that some such "washing out" of bone marrow elements occurred, in the presence of numerous erythroblasts and the bone-marrow giant cell (which I have found reported only once and that in pernicious anemia<sup>4</sup>). Moreover, there are two factors present which are known to increase the phagocytosis in these organs: pernicious anemia and transfusion. The increased phagocytosis in pernicious anemia, as is well known, has been emphasized especially by Warthin and by Hunter, who regard it as an essential feature in the pathology of the disease, a process to which the pigment deposits and bone-marrow changes are secondary. Hunter has also found

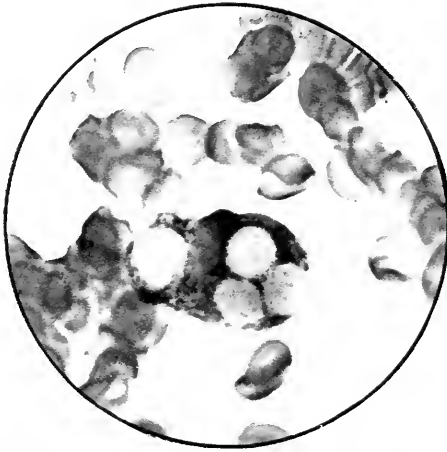


Fig. 6.—Phagocyte with four red cells. (Jenner stain:  $\times 1,000$ .)

these phagocytes in the portal circulation of animals poisoned with pyrogallol.<sup>5</sup>

As to the effect of transfusion, Gabbi,<sup>6</sup> as far back as 1893, found in transfusing from one normal rabbit to another, an enormous amount of phagocytosis in the spleen of the recipient, which he attributed to plethora. Aside from his work, which was not directed at this problem, there seems to be very little known as to the fate of the donor's cells after transfusion. Boycott and Douglas<sup>\*</sup> report that rabbit blood transfused into normal

4. Mosse: *Berl. klin. Wchnschr.*, 1907, xlv, 798.

5. Hunter: *Pernicious Anemia*, London, 1901, p. 176.

6. Gabbi: *Beitr. z. path. Anat. u. allg. Path.* (Ziegler's), 1893, xiv, 350.

<sup>\*</sup> Boycott and Douglas: *Jour. Path. and Bacteriol.*, 1910, xiv, 294.

rabbits is destroyed, and that the destruction is more rapid after repeated transfusions. They could not determine the mechanism of this destruction. In the blood charts in Crile's book on transfusion, it will be noted that in the successful cases, the blood-count the day after operation is often higher than that immediately afterward, or in other cases after a fall for two or three days there is then a gradual rise. Weber<sup>7</sup> and others have recently reported excellent results from the injection of small amounts of blood intravenously or even subcutaneously; and it has been suggested that transfused blood does not function directly in the recipi-

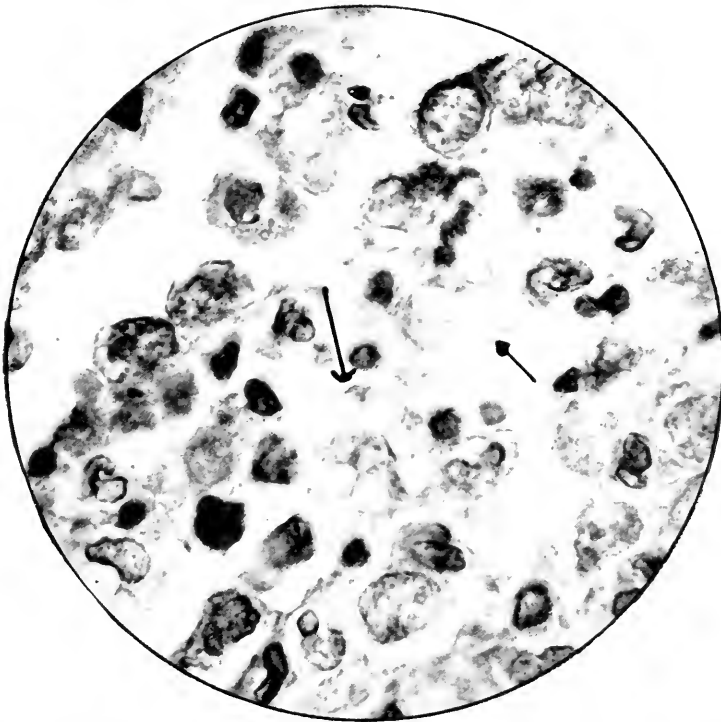


Fig. 7.—Mononuclear phagocyte containing eight red cells, from bone-marrow. (Hematoxylin-eosin;  $\times 1,000$ .)

ent, but acts by stimulating blood formation. Whatever may be the fate of transfused blood in most recipients, it has been noted by Crile and others that in pernicious anemia the count rises temporarily, and then falls rapidly to the previous level or below. The transfused blood is rapidly destroyed in these cases. Phagocytosis in the blood-destroying

7. Weber: *Deutsch. Arch. f. klin. Med.*, 1909, xevii, 165.

organs is usually performed by macrophages, but in this case the polymorphs may have taken part in the process and then have been washed into the circulation.

The phagocytosis might also be accounted for by the presence of an opsonin for human red blood cells. Savtchenko<sup>8</sup> found that the injection of inactivated serum of a rabbit immune to guinea-pig corpuscles, together with guinea-pig corpuscles, into the peritoneum of a guinea-pig, was not always followed by hemolysis, but sometimes by phagocytosis. Levaditi<sup>9</sup> found some phagocytes containing red cells in the circulating blood and great numbers in the spleen, after such injections. They attributed this action to the same *substance sensibilisatrice (fixateur)* that caused hemolysis, acting in this case in the absence of free cytase (alexin).

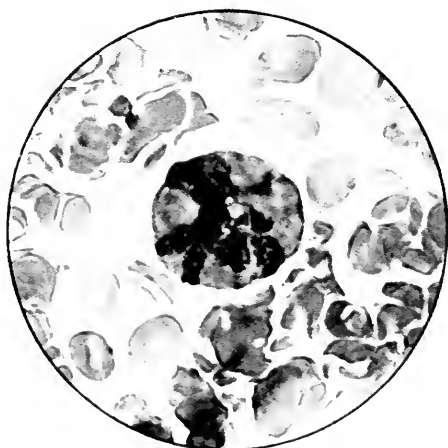


Fig. 8.—Phagocyte distended with red cells, too closely packed to be counted. (Jenner stain;  $\times 1,000$ .)

More recently, Barratt<sup>10</sup> and Keith<sup>11</sup> studied the same phenomenon *in vitro*, and demonstrated the same substance, which they regarded as a hemopsonin, in inactivated or diluted hemolytic serum. They found this body more sensitive to heat than the hemolytic amboceptor, and also found that it was quantitatively independent of the hemolysins or agglutinins, and concluded that it was a distinct substance. Neufeld and

8. Savtchenko: Ann. de l'Inst. Pasteur, 1902, xvi, 106.

9. Levaditi: Ann. de l'Inst. Pasteur, 1902, xvi, 233.

10. Barratt: Proc. Roy. Soc., London, 1905, lxxvi, B, p. 524.

11. Keith: Proc. Roy. Soc., London, 1906, lxxvii, B, 537.

Töpfer,<sup>12</sup> working independently, arrived at similar conclusions. Hektoen<sup>13</sup> has investigated the presence of isohemopsonins in human serums. He found them in a number of conditions, especially typhoid fever and scarlet fever; but not constantly in any condition; and it seems unlikely that they have any relation to disease. They occurred independently of agglutinins or hemolysins. Davis<sup>4</sup> and Macgregor<sup>5</sup> found these bodies in cases of cerebrospinal meningitis. Wright<sup>14</sup> reported phagocytosis in two cases of pneumococcus infection, and Eason<sup>15</sup> and later Kämmerer and Meyer<sup>16</sup> have reported autohemopsonins in cases of paroxysmal hemoglobinuria.

The observations of Dudgeon, Panton, and Ross<sup>17</sup> on guinea-pigs injected with hemolytic and cytotoxic rabbit sera show a condition which may have a bearing on our case. In the spleen of these animals they found "an extreme amount of phagocytosis, the large endothelial cells being packed with red blood cells and golden brown pigment." Great numbers of similar phagocytes were found in the mesenteric lymph nodes, a few in the liver and bone marrow, but none in the peripheral blood. This was, of course, an instance of autophagocytosis due possibly to an opsonin in the hemolytic serum.

I obtained serum and cells from this patient post-mortem, but could not demonstrate any opsonin in his serum for cells of several normal individuals, including the donor. The post-mortem serum did not agglutinate the donor's corpuscles. I also tested the serum of two other cases of pernicious anemia, which were negative. The serum of the donor contained no opsonin for cells of a normal individual or for those from a case of pernicious anemia. Serum from a normal individual contained no opsonins for the patient's red cells. These negative results, however, do not exclude the presence of an opsonin in the recipient's serum before transfusion. Such a body would doubtless have been bound by cells of the donor, and it is not surprising that it could not be found free in the serum a few hours later. The agglutinins present when the serum was first examined were evidently bound in this way.

12. Neufeld and Töpfer: *Centralbl. f. Bakteriol.*, 1905, Orig. xxxviii, 456.

13. Hektoen: *Jour. Infect. Dis.*, 1906, iii, 721; 1907, iv, 297.

4. Davis: *Jour. Infect. Dis.*, 1907, iv, 558.

5. Macgregor: *Jour. Path. and Bacteriol.*, 1909, xiv, 184.

14. Wright: *Brit. Med. Jour.*, 1906, i, 143.

15. Eason: *Edinburgh Med. Jour.*, 1907, xxi, 440.

16. Kämmerer and Meyer: *Folia Haematol.*, 1909, vii, 91.

17. Dudgeon, Panton, and Ross: *Proc. Roy. Soc. of Med.*, 1908-09, Path. Section ii, part 3, p. 64.

The fact that the phagocytes in this case were polynuclears would make it probable that the process was due to an isohemopsonin. In view of this experience it would seem advisable to test for opsonins as well as for lysins and agglutinins in cases in which transfusion is proposed.

In conclusion, I thank Drs. Janeway and Lyle for permission to report this case and for the clinical notes. I also thank Dr. F. C. Wood and Dr. Hans Zinsser for their advice and suggestions.

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## THE PROGNOSTIC SIGNIFICANCE OF PULSE-PRESSURE CHANGES DURING HEMORRHAGE\*

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Hemorrhage is a pathological process in which all organs suffer in function from the loss of blood, and the severity of the case depends not only on the quantity of blood lost, but also on the ability of the body to manage with that remaining. Consequently, our stock of facts for formulating a prognosis consists, first of all, of those data which indicate the degree that the body mechanisms are compensating and the extent to which the important functions are interfered with; and, in the second place, of those which indicate the progress of the bleeding itself. Thus the reaction of the higher nervous centers to the anemia is judged by the state of consciousness or stupor and the response of the corneal and pupillary reflexes, as well as the activities of the respiratory and cardio-inhibitory centers, as these are mirrored in the changed character of respiration and in the disturbances of cardiac rate and rhythm (Hayem,<sup>1</sup> Frédéricq.<sup>2</sup>) These signs, showing how well the body is enduring the hemorrhage, bear by no means a direct relation to the quantity of blood lost, nor to that remaining within the body, but, like immunity to infectious diseases, they vary, not only with race and species, but even in the same animal at different times.

Although the reactions of the body cells, many of them compensatory in character, are of great importance in prognosis and in indicating the management of the case, the prospects of ultimate recovery rest entirely on the probability of complete cessation of bleeding, for, obviously, the compensatory mechanisms cannot long remain active unless this occurs. But to a host of such questions as, "Has the hemorrhage ceased? Has it diminished, or has an exacerbation occurred?" the clinician can often supply no answer. This is owing, not only to the fact that hemorrhage

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\*Read in the Section on Pathology and Physiology of the American Medical Association, at the sixty-first annual session, held at St. Louis, June, 1910.

\*This investigation, the fourth in a series of studies in inaccessible internal hemorrhages, was carried out in the Physiological Laboratory of the University of Michigan.

1. Hayem: *Arch. de physiol. norm. et path.*, 1888, i, 106.

2. Frédéricq: *Travaux du Laboratoire de Liège*, 1885-1886; *Arch. de biol.* 1882, iii, 55.

is frequently associated with other pathological conditions (as for example, shock and infections), but as much to the fact that the results of experimental workers show very little relation between the signs and course of the bleeding. Thus, it has been established that the changes in height of blood-pressure, on account of the many interacting factors, bears no relation to the loss of blood (Worm-Müller,<sup>3</sup> Dawson,<sup>4</sup> Crile<sup>5</sup>). The same may be said of changes in heart-rate (Dawson<sup>4</sup>). A continued decrease in the percentage of hemoglobin or the number of red cells can also give no indication as to the course of bleeding, since both continue to decrease for several days after hemorrhage has ceased (Kiefer,<sup>6</sup> Dawson,<sup>7</sup> Crile<sup>5</sup>). This is particularly true in the case of large hemorrhages, in which a prompt diagnosis of the condition of hemorrhage becomes of the utmost importance.

It was with the hope that experimental methods might unearth some signs, which, by their changes, would offer a more rapid method of determining changes in the course of bleeding, that a series of experiments was carried out at the physiological laboratory at Ann Arbor, to determine the influence that hemorrhage or its cessation exerted on pulse pressure (that is, the difference between the systolic and diastolic pressures) and it seemed not unfitting to gather together the results, stripped as far as possible of technical details and adapted to trial in clinical cases.

This study of the behavior of the pulse-pressure during hemorrhage is preceded, to my knowledge, by only one other, that of Dawson,<sup>4, 8</sup> who found (1) that, while both systolic and diastolic pressures fell during hemorrhage, either might be affected more than the other or they could be equally affected, and (2) that while pulse-pressure always showed a marked diminution which corresponded in direction with the change in systolic output, it bore no relation to the percentage loss of blood. No attempt has hitherto been made to utilize changes in pulse-pressure as criteria of the direction in which the course of a hemorrhage is trending.

#### THE SYSTOLIC OUTPUT OF THE HEART DURING HEMORRHAGE

Normally the volume of blood contained in the large veins and auricles is always somewhat in excess of the quantity that can be accommodated in the right ventricle during its next diastole. Since blood leaves the vas-

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3. Worm-Müller: Ber. d. sassch. Gesellsch. der Wissensch., math. phys. Classe, 1873.

4. Dawson: Jour. Exper. Med., 1905, vii, 6.

5. Crile: Transfusion and Hemorrhage, 1909, New York, pp. 69, 100.

6. Kiefer: Med. News, London, 1892, ix, 225.

7. Dawson: Am. Jour. Physiol., 1900, iv, 1.

8. Dawson and Gorham: Jour. Exper. Med., 1908, x, 484.

cular system during hemorrhage, the quantity returned to the heart of necessity immediately diminishes, but, on account of the excess supply, the filling of the ventricle is not at once interfered with. Hence, a latent period, varying with the degree of bleeding from a few seconds to several minutes, intervenes between the beginning of hemorrhage and the time when the filling of the ventricle is effected (Fig. 1.) After this interval the ventricular filling becomes impaired, owing to the fact that the difference between the veno-auricular pressure and the pressure in the relaxing ventricle becomes less. The filling becomes more gradual during the period of active relaxation and extends into the period of diastasis, although the quantity injected by the auricles often remains practically unreduced. Thus it comes about that the auricular contraction, which normally contributes so little to the ventricular filling, may acquire one-half of that responsibility (Fig. 2). The systolic discharge lessens

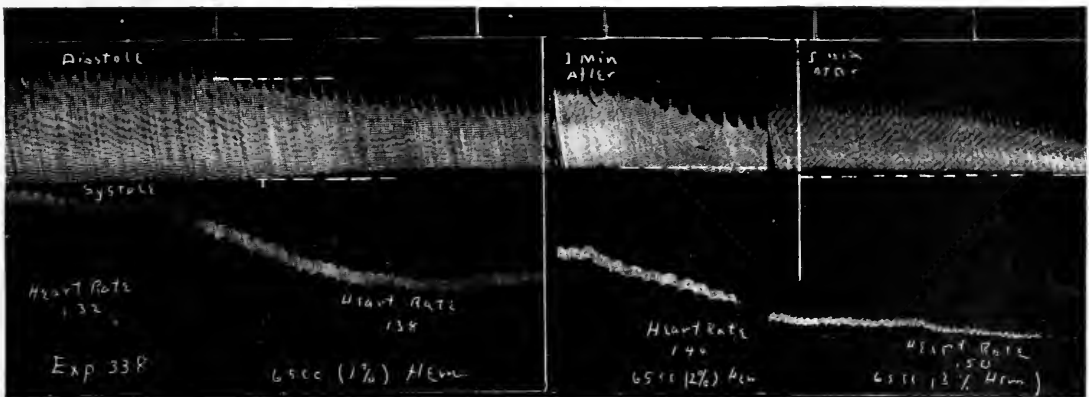


Fig. 1.—Effect of three hemorrhages and their cessation on the systolic output of the heart (upper curve) and the blood-pressure (lower curve). Heart-rate calculated from simultaneous record on faster drum.

during hemorrhage entirely as a result of this impaired filling. Even to the end, the nutrient supply of the heart is usually sufficient to enable it to carry on undiminished contractions. Incidentally, this observation shows that the fear, so often exhibited by physicians, lest the heart cease beating, is ungrounded, and that the administration of cardiac stimulants for this reason is quite unnecessary. As a matter of fact, the amplitude of contraction is often increased early in hemorrhage, causing the ventricles to empty themselves more completely.

When hemorrhage ceases, the supply of blood to the right heart increases with surprising rapidity. If hemorrhage stops suddenly, as in

the case of artificial hemostasis, the increase is immediate, owing probably to the increased arterial pressure which immediately follows the sudden occlusion of a bleeding vessel. If the occlusion occurs gradually through the natural process of clot formation, this influence is still felt, though to a diminished degree. In this case other compensatory mechanisms are chiefly responsible for the return of blood, these being the resorption of lymph by the capillaries and the modifying effect of the respiratory movements.

When the large veins are normally filled with an excess supply of blood, the act of inspiration may, by creating a negative pressure in the thorax, and by compressing the abdominal veins, favor the return of blood to the heart (de Jager<sup>9</sup>); but, according to Henderson,<sup>10</sup> it is mechanically impossible for this extra quantity to be pumped out except by an increased rate of beat. I am able to confirm, I believe, that normally

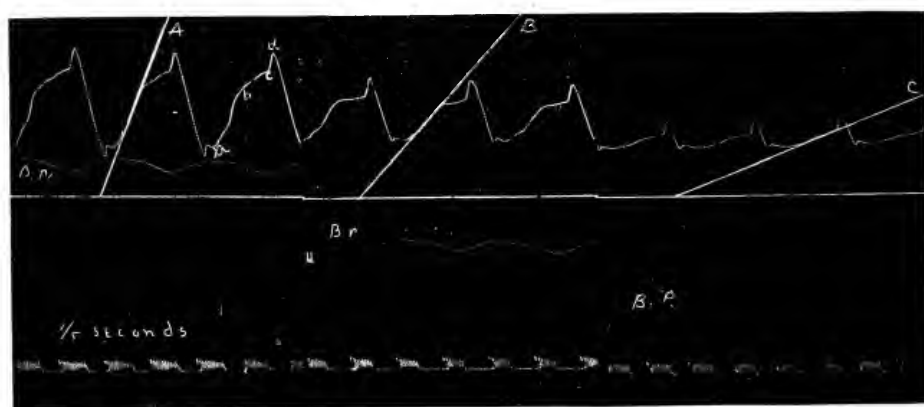


Fig. 2.—Effect of hemorrhage on the rapidity of ventricular filling, taken on a rapid drum from same experiment as Figure 1.

the increase in heart-rate during inspiration is largely responsible for the augmented output per minute during that respiratory phase, but can not agree that respiration does not modify the filling of the ventricle. My records, as well as some of those published by Henderson, to my eye, indicate that the rate of ventricular filling during early diastole is less rapid in inspiration than in expiration. On account of the removal of the normal vagus tonus during hemorrhage, the respiratory variations in heart-rate are abolished and, therefore, the changes occurring as a result

9. De Jager: *Arch. f. d. ges. Physiol.*, 1884, xxiii, 17; *Jour. Physiol.*, 1886, vii, 194.

10. Henderson: *Am. Jour. Physiol.*, 1906, xvi, 344.

of the intermittent quickening and slowing of the heart are absent. The variations which now take place in the systolic output are entirely to be accounted for by the altered filling during inspiration and expiration. The greater return of blood to the chest at the end of inspiration and the beginning of expiration results in a more prompt and complete filling of the ventricle during diastole (Fig. 3), the inflow becoming more rapid during the period of active relaxation, while the period of diastasis may be changed from one of gradual filling to one of practically no filling.

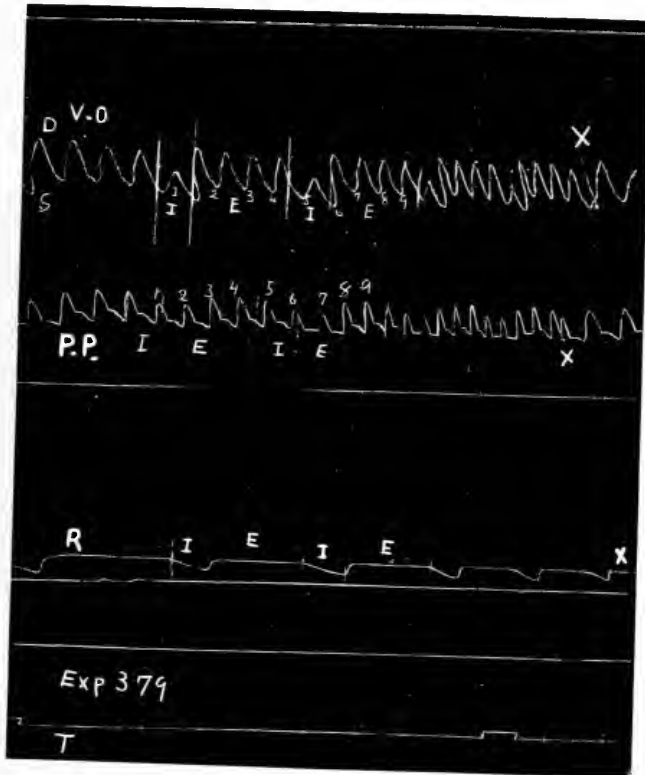


Fig. 3.—Showing more rapid and consequently more complete filling of ventricle during beginning of expiration. V. O., ventricular output; S, systole; D, diastole; P. P., pulse-pressure taken with a Hürthle manometer; R, respiration, the lever moving down in inspiration; T, time in seconds; X, relative position of writing levers.

When the duration and extent of hemorrhage become marked, this effect may be intensified by an augmentation and acceleration of the respiration. If expiration becomes forcible, the abdominal veins are compressed not only by the descent of the diaphragm in inspiration, but also by the

contraction of the abdominal muscles in expiration (Fig. 4). In all these ways respiration favors the return of blood to the large veins and auricles, and rhythmically augments the filling of the ventricles. This filling may furthermore be aided by a compensatory contraction of the auricle itself. Almost without fail, the filling of the ventricles and, in a corresponding measure, the systolic output are rapidly increased as soon as hemorrhage

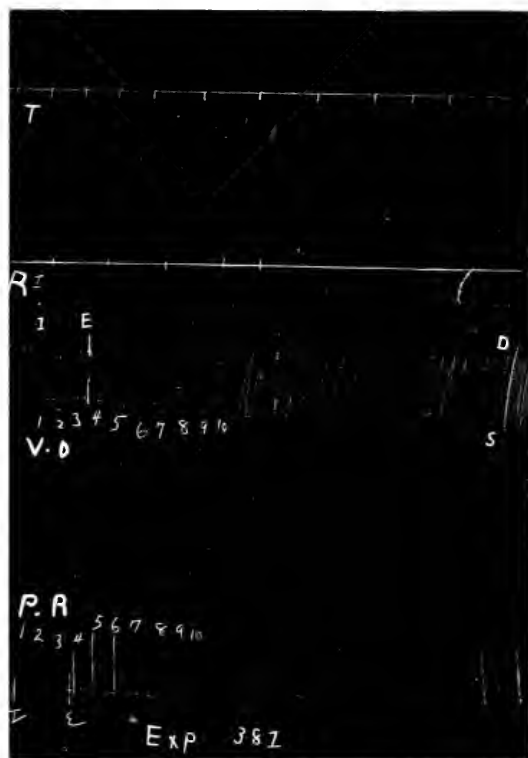


Fig. 4.—Showing that forced expiration aids filling of ventricle. Lettering same as before.

ceases, as the compensatory mechanisms can now exert themselves without opposition. This never occurs so long as bleeding continues, for they are not able to overpower the effect of a continued drain of blood.

#### THE PULSE-PRESSURE AS AN INDEX OF SYSTOLIC OUTPUT

Having determined primarily that changes in the systolic output correspond with a fair degree of rapidity to changes in the course of a hemorrhage, the next query directed itself quite naturally to the question

of how accurately changes in systolic output were revealed by the pulse-pressure.

Dawson and Gordon<sup>8</sup> recorded simultaneously tracings of the pulse-pressure and volume changes in the ventricles. Their tracings showed that under various conditions, hemorrhage included, a close correspondence occurred in their general course. They therefore concluded that the pulse-pressure might be taken as an index of the systolic discharge. Henderson, restudying the subject, pointed out, however, in his own data as well as in those submitted by Dawson and Gordon, that the pulse-pressure and systolic output bear a widely varying ratio to each other at different times, and hence he concluded that the pulse-pressure was not an accurate index of the systolic discharge.

In more than twenty experiments in which the pulse-pressure tracings taken by a Hürthle manometer were compared with the volume output of

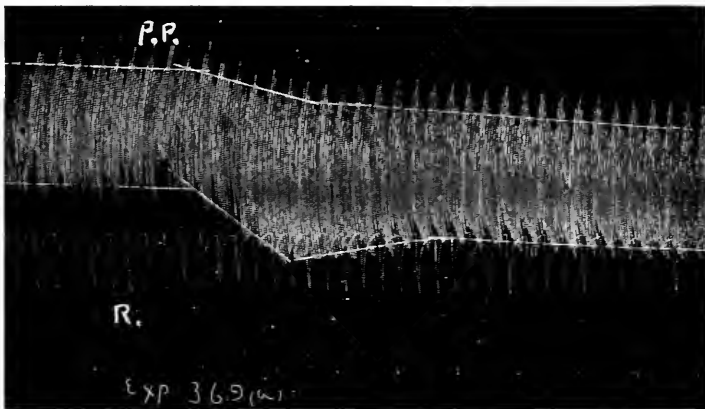


Fig. 5.—Effect of large hemorrhage on pulse-pressure obtained from femoral. Lettering same as before.

the ventricles recorded from a cardiometer, in principle that of Henderson's, it was found that, in general, the two tracings followed each other so closely during a hemorrhage that by covering one it was possible to prophecy the course of the other. Consequently, it seems that the clinician who follows the pulse-pressure changes within short intervals of time (5 to 10 minutes) obtains a general idea from his observations as to whether the systolic output is increasing or decreasing. Henderson's criticism, however, holds true during hemorrhage, for the same pulse-pressure may, at different times, be accompanied by differing systolic discharges. Hence, the clinician is not warranted in assuming that, because the pulse-pressure is equal to that obtained at some other time, the sys-

tolic discharges were equal. The pulse-pressure is never a quantitative measure of the systolic output; but, *when compared to some immediately preceding observation, may generally be used as a qualitative indication of the direction in which the systolic discharge varies.*

Exceptions to this statement, however, must be recorded. In the case of a large hemorrhage, the diastolic pressure suddenly falls and causes an increase in pulse-pressure, although the systolic output actually decreases (Fig. 5). This is due to the sudden lowering of resistance which the rupture of a large vessel causes, for as shown by Hürthle,<sup>11</sup> the pulse-pressure increases with a decreased and decreases with an increased peripheral resistance. Careful statistical analysis of those curves in which pulse-pressure and cardiac output per beat follow in the same direction shows that, early after the inception of the bleeding, the pulse-pressure is larger in proportion to the systolic output than later, when



Fig. 6.—Respiratory variations in pulse-pressure during hemorrhage. Lettering same as before.

the hemorrhage tends to cease. This may be accounted for by the fact that, as hemorrhage proceeds, the peripheral resistance is raised, not only by a general vasoconstriction, but also by the formation of a clot over the wound. After the bleeding has entirely ceased, the pulse-pressure may again become proportionately larger, a fact probably to be explained by a lessening of the viscosity of the blood, which occurs when the plasma is replenished by absorbed lymph. While the pulse-pressure may thus be affected by the changes in peripheral resistance, this factor is not sufficiently pronounced to cause it to deviate in direction from the systolic

11. Hürthle: Arch. f. d. ges. Physiol., 1888, xliii, 433.



output, except when the hemorrhage is very large. Even in this case the comforting fact remains that this increase is very temporary and is soon replaced by a progressive decrease.

As a second exception it must be mentioned that augmented and forcible respirations will rhythmically cause a marked augmentation of the pulse-pressure, as recorded by a Hürthle manometer, a change that is due chiefly to a periodic increase of the systolic pressure (Fig. 6). In such cases an average of these pressures may probably be considered an output index comparable with systolic discharges, when no such marked variation occurs. When such a comparison is made, however, it is found that the average pulse-pressure often shows an increase when no corresponding increase in systolic output is found. Hence, augmentation of the pulse-pressure, as determined by clinical instruments, when accompanied by forcible expirations, loses its value as a criterion of the degree of bleeding, for, by such instruments, we can obtain only the average pulse-pressure. In the common method of estimating the systolic pressure by palpating for the return of the pulse at the wrist, the first few "rudimentary" waves (von Recklinghausen<sup>12</sup>) are missed by the palpating finger (Janeway<sup>13</sup>) and, accordingly, the pressure read is never the highest occurring during a respiratory phase, but probably approximates an average. Since the diastolic variations are not marked, they can, for that reason, probably be disregarded without detriment to the results. Subtraction of this diastolic pressure from the average systolic pressure evidently gives a result approximating an average pulse-pressure.

*Summary.*—A progressive decrease in pulse-pressure indicates a continuance of the hemorrhage. An increase may signify, (1) that hemorrhage continues, but that the effect of respiration has interfered with its true relation to the previous pulse-pressure; (2) that hemorrhage has ceased; or, (3) that it has become exacerbated. The existence of augmented respirations can be ascertained by observation, but the fact that the same change may indicate either a cessation or a great augmentation is, at first thought, not encouraging for establishing a prognosis. It is, however, possible to differentiate. An increase in pulse-pressure due to an augmentation of hemorrhage is temporary and is soon supplanted by a marked decrease, whereas an increase due to cessation of hemorrhage remains permanent at subsequent measurements. Furthermore, the heart becomes accelerated (unless already very rapid) if the hemorrhage has increased, whereas no such change accompanies a cessation.

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12. Von Recklinghausen: *Arch. f. exper. Path. u. Pharmacol.*, 1901, xvi, 103.

13. Janeway: *The Clinical Study of Blood-Pressure*, 1904, p. 62.

## THE MINUTE OUTPUT DURING HEMORRHAGE

Experimental investigations (Henderson<sup>10</sup>) have satisfactorily established that an acceleration of the heart may itself act to reduce mechanically the output of blood per beat. Since during hemorrhage the heart-rate increases, the question naturally arises, "How is it possible to determine whether the reduction of pulse-pressure is due to a loss of blood, or is a natural consequence of the cardiac acceleration?" A determination of the volume of blood discharged by the ventricle per minute, or the minute output, as it may concisely be styled, offers a means of differentiation. This systolic output per minute may, in the case of regularly beating hearts, be determined experimentally by multiplying the systolic output by the number of beats per minute. Since the pulse-pressure gives a qualitative indication of the changes in systolic output occurring in consecutive intervals, the variations in minute output may be followed by obtaining the product of the pulse-pressure and heart-rate. Henderson has shown, however, that if the acceleration of the heart is not too great, the minute output will always *increase as the heart-rate increases*. During hemorrhage the minute output, as estimated by the product of systolic discharge and heart-rate, *always decreases as the heart accelerates*. Consequently, the product of the pulse-pressure and heart-rate may also be expected to decrease as the heart-rate becomes more rapid. Experiments show this to be the case, except in the two instances before pointed out, in which the pulse-pressure was not changing in the same direction as the systolic output, that is, during markedly augmented respirations and at the beginning of very large hemorrhages. In these cases the product increases.

## CONCLUSION

While there are interfering factors which may at times mask the significance of pulse-pressure changes, the deduction may be drawn that many cases of hemorrhage must occur in practice in which these pulse-pressure changes may be of value in following the course of bleeding.

The following series of procedures may then be recommended for following the course of a suspected or diagnosed internal hemorrhage:

1. Eliminate as far as possible psychical factors in the patient by the administration of the customary dose of morphin.
2. Determine the systolic and diastolic pressures by means of the sphygmomanometer at intervals of not more than ten minutes, and more frequently if possible. By subtraction obtain the pulse-pressure. Also determine the rate of the pulse and respiration.

3. Tabulate the data as the observations continue. If the respirations undergo little or no change, the following deductions may be drawn: A: A progressive decrease in pulse-pressure and decrease in the product of the pulse-pressure and the heart-rate indicate a continuance of the bleeding. B: An increase of both, if permanent, after several determinations, indicates a cessation of hemorrhage. C: A temporary increase of both, followed by a marked decrease on subsequent examinations, indicates an exacerbation.

If it is true, however, that such determinations possess a clinical value, the fact should be capable of demonstration in a similar manner on animals. I have not, as yet, had time to test my skill in following the course of a sufficient number of such hemorrhages to draw final conclusions, but the results incorporated in the table appended give an indication of the close correspondence in a number of cases. In these experiments hemorrhages were produced in dogs by an assistant, at intervals and times unknown to me. With maximal and minimal manometers I determined at various intervals the data, as outlined above, incorporated them in the table, made my predictions, and compared them with the actual state of hemorrhage. Since these experiments are so few in number, I shall refrain from remarks concerning them, except to state that they are suggestive of future possibilities.

TABLE OF PULSE-PRESSURE CHANGES IN CONNECTION WITH HEMORRHAGES  
EXPERIMENT 369, FEB. 27, 1910

Time.	Heart Rate.	Systolic Pressure.	Diastolic Pressure.	Pulse Pressure	Minute Output	Predicted Course of Hemorrhage.	Actual Course of Hemorrhage.
3:00	110	90	62	28	3080	.....	.....
3:05	126	62	46	16	2016	Hemorrhage started.	Hemorrhage lasted
3:13	126	72	58	19	2394	Hemorrhage stopped.	3.03 to 3.06.
3:18	126	42	33	6	756	New hemorrhage.	Hemorrhage lasted
3:32	126	64	40	24	3024	Hemorrhage stopped.	3.15 to 3.19.
3:38	144	68	42	26	3744	.....	.....
3:40	156	39	24	8	1248	Large hemorrhage.	Hemorrhage lasted
3:50	150	37	27	10	1500	Decreased:	3.38 to 3.41.
4:02	150	28	18	10	1500	Continued:	.....

## PULSE-PRESSURE CHANGES DURING HEMORRHAGE

## EXPERIMENT 377, APRIL 12, 1910

Time.	Heart Rate.	Systolic Pressure.	Diastolic Pressure.	Pulse Pressure.	Minute Output*	Predicted Course of Hemorrhage.	Actual Course of Hemorrhage.
4:00	150	137	68	69	10350	.....	.....
4:02	156	142	67	75	11700	.....	.....
4:05	162	131	63	68	11016	Hem. started? Yes.	Hemorrhage lasted
4:10	162	124	63	61	9882	.....	4.04 to 4.14½.
4:15	162	116	62	54	8748	.....	.....
4:17	162	122	64	58	9339	Hemorrhage stopped.	.....
4:29	162	116	57	59	9458	.....	.....
4:51	162	111	55	59	9458	Small hemorrhage?	.....
4:37	156	112	52	60	9360	No.	.....
4:39	162	94	50	44	7128	Exacerbation.	Hemorrhage lasted
5:01	162	78	44	34	5508	Continued.	4.37 to 4.40.
5:03	162	84	42	42	6809	Stopped.	.....
5:06	162	68	37	31	5022	Exacerbation.	Hemorrhage lasted
5:10	144	48	30	18	2892	.....	5.06 to 5.10.

## EXPERIMENT 378, APRIL 13, 1910

3:30	114	114	67	47	5358	.....	.....
3:34	114	86	49	37	4218	Hemorrhage started.	Hemorrhage lasted
3:38	132	80	44	36	4752	Hemorrhage stopped.	3.30 to 3.34.
3:42	126	69	42	27	3402	Hemorrhage started.	Hemorrhage lasted
3:44	126	69	44	25	3150	.....	3.38 to 3.39.
3:46	129	73	40	33	3960	Hemorrhage ceased.	.....
3:49	129	61	39	22	2640	Exacerbation.	Hemorrhage lasted
3:51	129	48	32	16	1950	.....	3.39 to 3.46.

## EXPERIMENT 379, APRIL 16, 1910

4:10	111	82	38	44	5016	.....	.....
4:11	108	84	38	46	4968	.....	.....
4:13	108	71	34	37	3906	Hem. in progress.	Hemorrhage lasted
4:14	108	72	36	36	3886	.....	4.12 to 4.14.
4:16	108	73	36	37	3990	Hem. diminished.	.....
4:18	114	73	34	39	4446	Large exacerbation	Hemorrhage lasted
4:20	114	56	30	26	2964	Large hemorrhage.	4.18 to 4.21.
4:23	114	57	32	25	2850	.....	.....

\* Minute output estimated by product of pulse-pressure and heart-rate.

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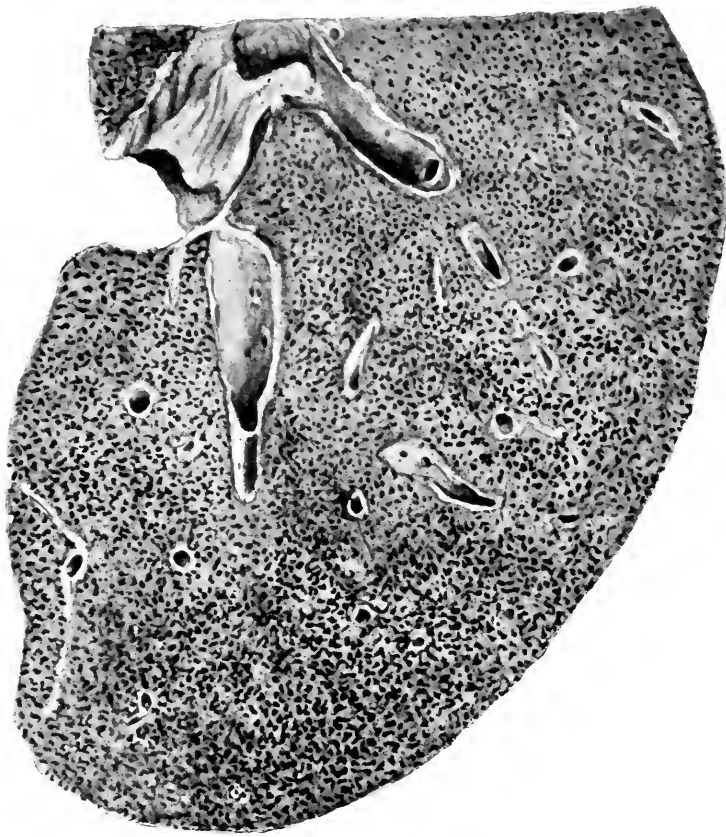


Fig. 1.—Section of liver.

# MULTIPLE NON-INFLAMMATORY NECROSIS OF THE LIVER WITH JAUNDICE IN CHRONIC CYANOSIS\*

HORST OERTEL, M.D.  
NEW YORK

## HISTORY OF CASE

A man, 25 years old, entered Dr. Potter's service at the City Hospital, on Sept. 3, 1909, with typical symptoms of mitral stenosis and evidences of general stasis. These symptoms became aggravated and the patient rapidly developed considerable edema, fluid in his chest, pulsating veins and pulsating and distinctly enlarged liver.

On October 8 there was observed for the first time faint jaundice; the leucocyte count was then 8,400. On the 11th the jaundice had become marked, and there was occasional vomiting of brown fluid. The stools were formed, brown and contained blood. On the 13th, he had epistaxis and considerable blood in his sputum. On the 16th, his jaundice had deepened; there was hemorrhage from the bowels. The stools were loose, yellowish and contained mucus. He rapidly became weaker and died with deep jaundice on October 18. The fatal period was unaccompanied by any rise in temperature. The clinical diagnosis was mitral stenosis, general stasis and doubtful infectious cholangitis.

## AUTOPSY

The autopsy disclosed a mitral stenosis due to fibrous vegetative endocarditis, moderate hypertrophy of the left, and marked hypertrophy and dilatation of the right side of the heart. The other heart valves were well preserved. Double hydrothorax, emphysema and edema of the lungs with numerous infarctions were present. All viscera showed the effects of severe cyanosis. The abdominal cavity contained a liter of dark, reddish-brown fluid. The liver came to the costal margin. There was slight distention of the gall-bladder, with a few adhesions around the common duct. The larger bile ducts were entirely free. The liver itself weighed 1,000 gm. and measured 23 cm. by 12 cm. It was smooth and distinctly greenish jaundiced.

## MICROSCOPIC EXAMINATION

On section, the liver cuts easily. Its cut surface is smooth, and while the normal markings have entirely disappeared, it shows a distinct pattern of plump, occasionally anastomosing hemorrhagic spots and streaks on a distinctly greenish ground color. In places, these hemorrhagic markings are obliterated, or at least much lessened, by a more uniform, rather turbid, pale greenish color (Figure 1).

Microscopical examination shows a picture very similar to what I have elsewhere described<sup>1</sup> as a lesion entirely distinct from the result of uncomplicated stasis. (The latter is illustrated for comparison in Fig. 2.)

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\* From the Russell Sage Institute of Pathology.

\* Presented to the Section of Internal Medicine of the New York Academy of Medicine, April 19, 1910.

1. Oertel, Horst: A Further Contribution to the Knowledge of Multiple Non-Inflammatory Necrosis of the Liver With Jaundice, Jour. Exper. Med., 1906, viii.

The normal lobular structure has given way to an irregular, streaky central necrosis and disorganization of the liver lobules. The central veins are dilated, within completely necrosed areas occasionally collapsed; their walls are frequently hyaline and swollen. The areas around the central veins show destruction of the liver cells, leaving an irregular reticulum enclosing protoplasmic remains, pale nuclei, blood pigment and some bile clumps with fat drops. Between the collapsed liver cells are occasionally to be seen engorged blood capillaries. In the completely destroyed parts are marked hemorrhagic extravasations. The importance of the latter varies: sometimes free blood is striking and lies diffuse within pale necrotic masses, when it fairly controls the field; again, it appears in rather irregular patches, separated by necrotic masses; in places, it is still to be seen within enormously engorged capillaries in otherwise collapsed areas. This hemorrhagic extravasation is entirely confined to the necrotic portions and stops quite abruptly toward the better-preserved liver cells at the periphery of the lobule (Fig. 3). Between these necrotic areas and the preserved liver cells which form the periphery of the lobule, there is an irregular zone of distinct, usually large drop fat infiltration which radiates in some columns toward the periphery (Fig. 4).

While the origin of the lesion appears distinctly around the central veins, the distribution, like that observed in advanced cases of stasis, is irregular and, in streaky fashion, runs from one lobule into the other. The liver cells at the periphery of the lobules show edematous swelling, occasionally beginning vacuolization of their protoplasm, and are closely packed (Fig. 5). Around the necrotic focus are dilated blood and bile capillaries. Intracellular bile capillaries filled with bile are occasionally prominent, but not excessive. Particular emphasis is to be laid on the fact that the portal spaces and bile ducts are entirely free. They show only engorged blood-vessels.

Of interest here, as in the cases previously described, is the type and subsequent course of the necrosis, which is not that usually observed in the inflammatory destructions of the liver tissue, with formation and coagulation of dead protoplasmic masses. It appears primarily to be an edematous solution of the compressed central liver cells between engorged capillaries.

Early in this process, the affected cells appear studded with fine bile granules. The disintegrating protoplasmic masses, however, appear to undergo a rapid solution, fading and fatty metamorphosis. The nucleus, which is affected much later, shows evidences only of gradual solution and chromatolysis, without any characteristic degenerative features. The reticulum is retained towards the last, so that this is still conspicuous and definite in the lobules in which the central cells have completely disappeared. Fibrin could not be demonstrated in these sections.

Clinically and anatomically this case, like those previously described, differs essentially from the results of uncomplicated stasis and stands sharply outlined. Clinically, it could be well differentiated by a progressing jaundice, grafted on severe venous stasis; in some cases previously observed, stupor, delirium and coma prevailed; anatomically, by the peculiar cytolytic central necrosis with hemorrhagic extravasations within



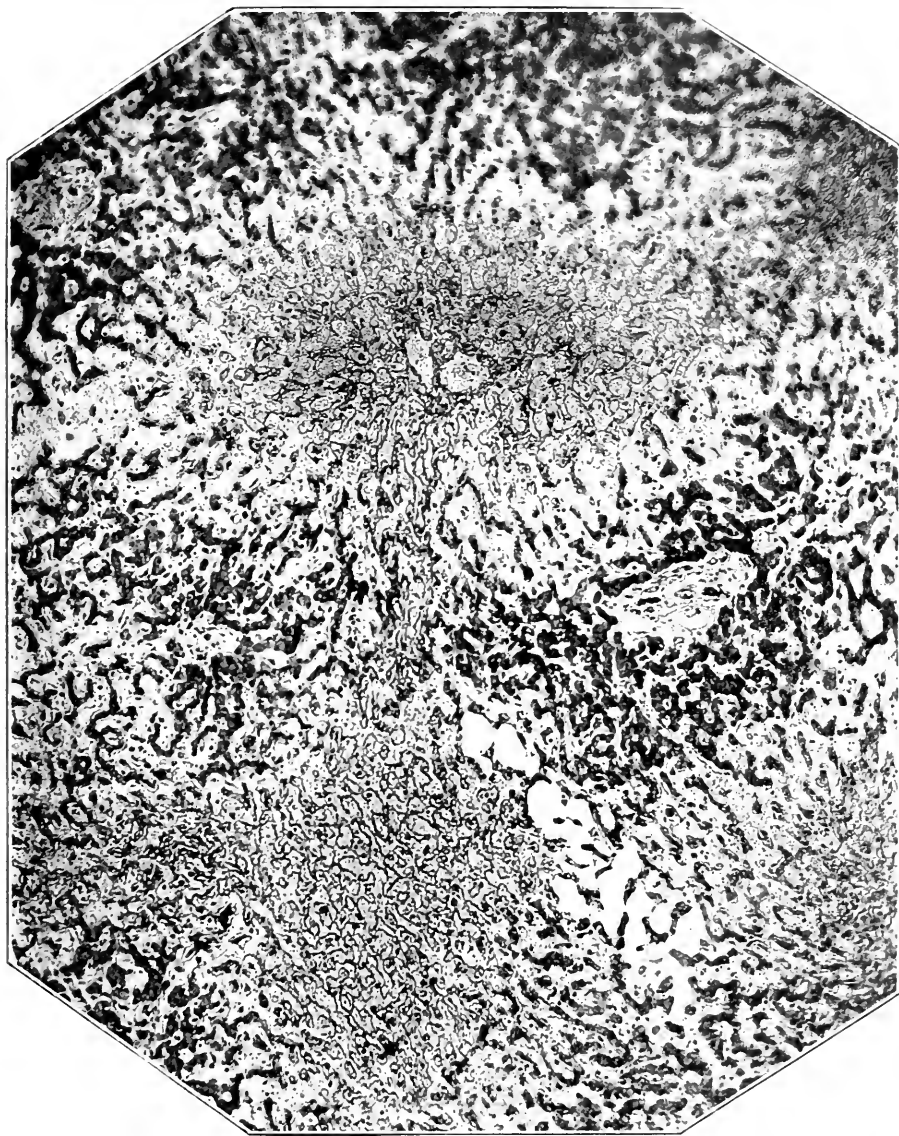


Fig. 2.—Specimen from a case of advanced, uncomplicated venous stasis (red atrophy) of the liver. Enormous dilatation and fibrillar thickening of and around the central veins with extreme engorgement of the blood capillaries in the center of the lobules; complete atrophy of the liver cells in this area. The middle zone of the lobules shows marked atrophy and separation of the liver cells, while at the periphery they are better preserved. Portal space somewhat edematous, otherwise intact. This figure is inserted here for the sake of comparison.  $\times 100$ .

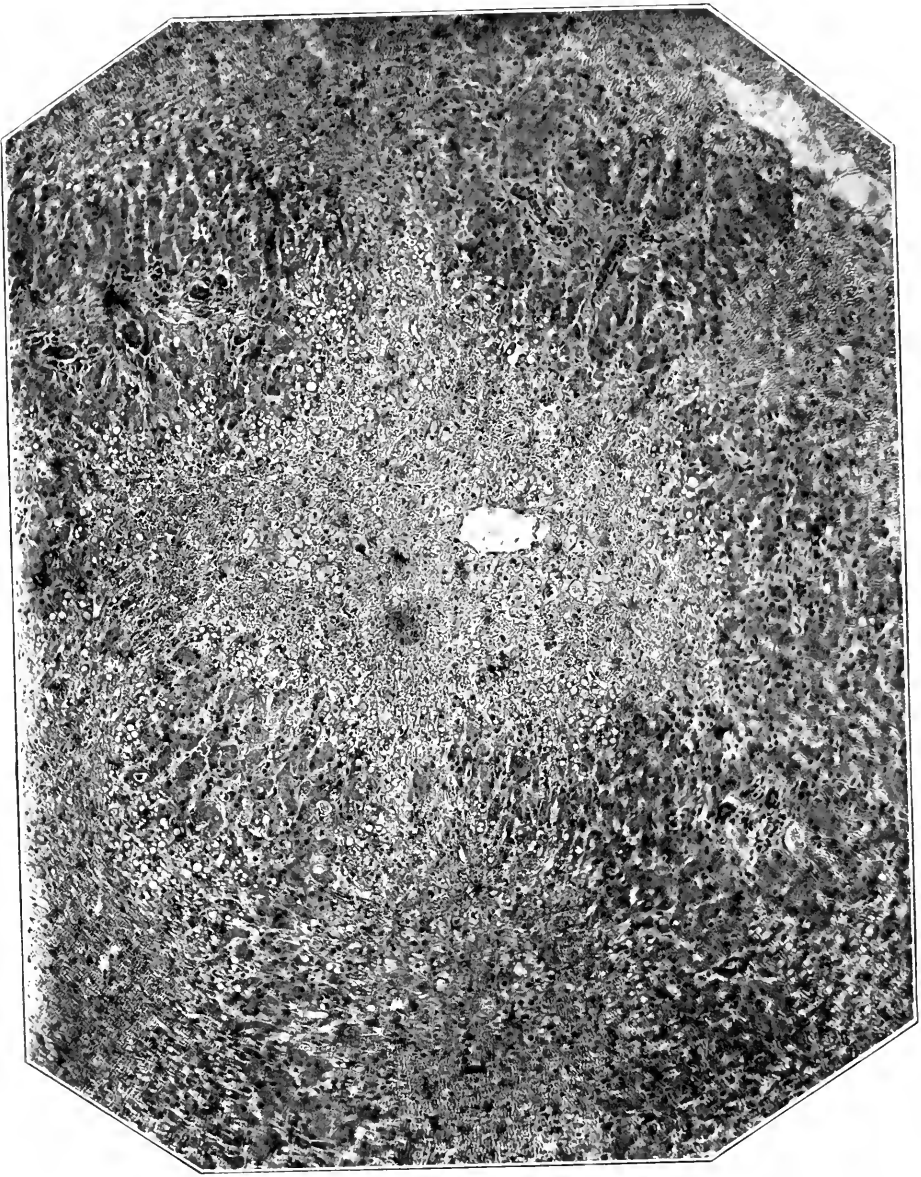


Fig. 3.—Specimen from case of cyanosis with necrosis and jaundice. Central necrosis of the liver lobules around the dilated veins, leading to destruction of the architectural arrangement of the lobule and leaving a reticulum with extravasated blood pigment, nuclear and protoplasmic remnants. The middle zone of the lobule shows pronounced fat infiltration with swelling and gradual solution of the liver cells. At the periphery of the lobule, where the liver cells are best preserved, they appear swollen and separated by dilated blood and bile vessels. Portal spaces and bile ducts free.  $\times 100$ .

these areas and moderate bile imbibition. Noteworthy is the central fat infiltration with absence of any such involvement at the periphery of the lobule and a relatively sharp line of demarcation between the necrotic areas and the edematous, swollen cells composing the periphery of the lobule. Unlike the simple pigmentary atrophy in uncomplicated stasis, this process leads rapidly to entire destruction of the architecture of the involved parts.

In tracing the genesis of this lesion, as well as its character, one must consider primarily its relation to chronic cyanosis. There can be no question that this preceded the changes here described. Originally, I was not inclined to think that the stasis stood in direct genetic relation to the necrosis and jaundice, but rather regarded these as the result of a toxic invasion. Continued studies, however, have associated the lesion so definitely with cases of advanced venous congestion, and it follows so strictly in its paths, that a direct relation is made extremely probable.

Two possibilities must be taken into consideration: One, that the lesion represents an additional infection, which follows in the path of least resistance; investigations for bacteria have not, however, disclosed any support for this view, and the absence of any inflammatory reaction on the part of the liver would also argue against it. On the other hand, it may be assumed with some justification that during the process of cell atrophy and stasis, a formation of cytolytic ferments occurs, which inaugurates the terminal lesion. The passive features of the process, which are so characteristic, support this view, as well as the peculiar type of cellular destruction. The lesion may, therefore, be interpreted as a severe continued cyanosis of the liver, leading to central, non-inflammatory lytic necrosis and blood extravasations into the affected liver lobules, which, in general, follow the distribution of the stasis. The rapidly supervening jaundice must depend on the terminal rapid destruction of liver tissue with necessarily associated intralobular bile stasis.

In favor of this, on the one hand, is the entire absence of a discoverable cause or existence of any bile obstruction outside of the lobules, and freedom of the portal bile-ducts from disease; on the other hand, the straight morphological evidence of liver-tissue destruction with purely lobular capillary bile stasis.

These points also eliminate the possibility of any genetic relation of the jaundice to the liver necrosis, a factor one would naturally think of, in the light of our knowledge of the lytic qualities of the bile. In this regard, it is also interesting to know that the degree of bile imbibition in the affected lobules stands in no direct relation to the extent of the necrosis.

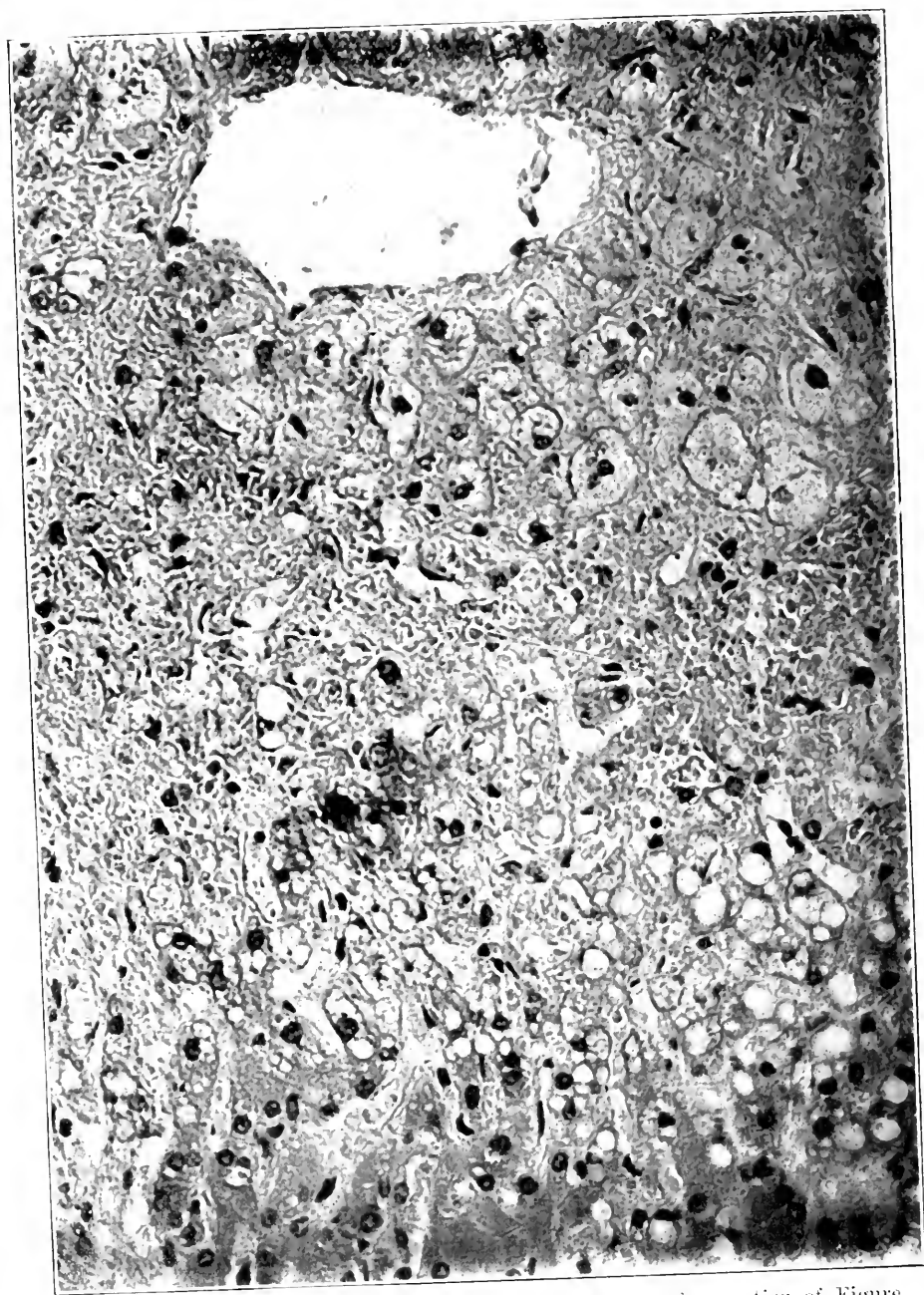


Fig. 4.—Specimen from high magnification ( $\times 400$ ) of a portion of Figure 3, in the immediate vicinity of the dilated central vein, illustrating complete destruction of the central part of the lobule, leaving a reticulum enclosing protoplasmic remnants and nuclei. Between this reticulum partly dilated capillaries are engorged with blood; in the middle zone of the lobule streaky, free blood extravasation with fat infiltration which becomes more marked toward the periphery, where it meets the swollen but better-preserved cells.

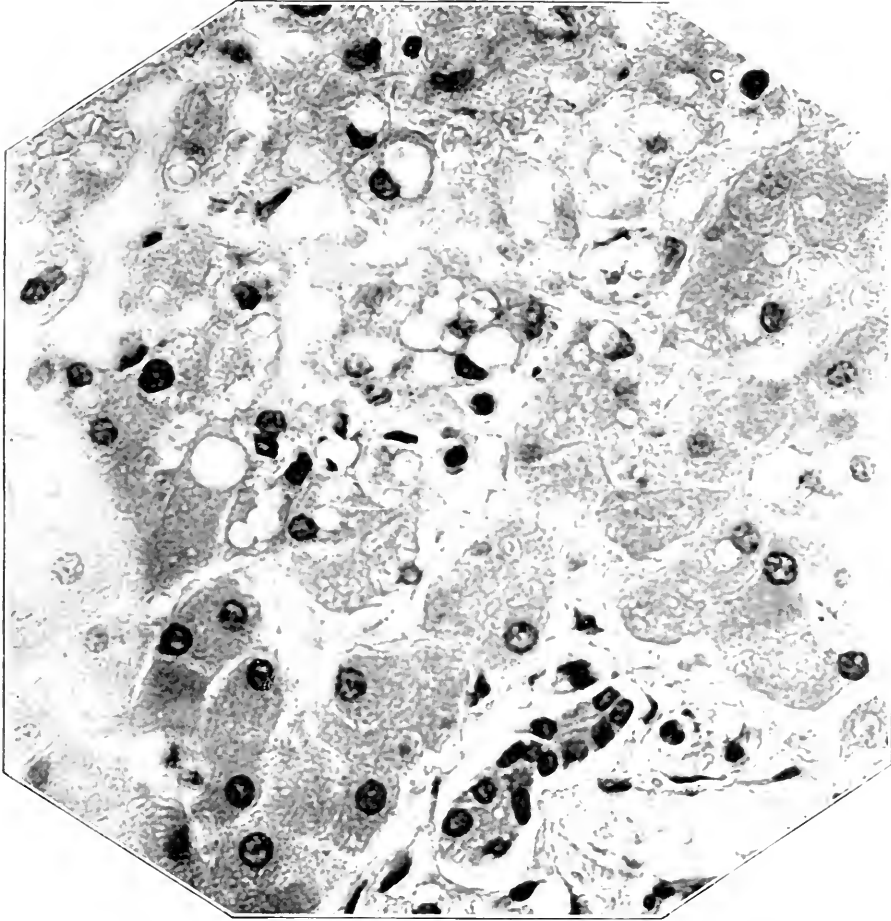


Fig. 5.—From a high magnification ( $\times 500$ ) of periphery of a lobule showing extension of fat infiltration of the liver cells from the middle zone, with gradual solution of their protoplasm and nuclei. The liver cells in immediate vicinity of a portal space, with an intact bile duct, are markedly swollen and very closely packed. In places their protoplasm shows beginning solution and chromatolysis of the nucleus.

In the cases previously observed in the Russell Sage Institute, the degree of jaundice has shown a considerable variation, from a faint yellow to a deep greenish yellow. Characteristic of its clinical course is rapid deepening after it once has made its general appearance. Patients have died, however, and come to autopsy before the latter had become accentuated. Recovery seems doubtful, for all patients so far observed died.

The central fat metamorphosis, which is particularly marked in the zone between the completely disorganized liver tissue and the free peripheral cells, deserves consideration. In contradistinction to the usual peripheral fatty infiltration, central fat metamorphosis occurs with frequency in certain toxic lesions; some poisonings, like phosphorus, etc., also acute and subacute atrophies, in severe anemias and cachexias. It may be assumed that, on account of the circulatory conditions within the lobules, the cells suffer there primarily and most severely. Its characteristic location in this case might possibly, at least partly, represent a resorption of fatty compounds from the disintegrating autolyzing central focus. It is a question of interest whether this possibility applies to other toxic lesions associated with distinctly central fatty metamorphosis of the liver, as the severe anemias and the acute and subacute atrophies. This would then differentiate them from the usual irregular peripheral portal fat infiltrations in simple nutritive disturbances of the liver. The solution of this problem, however, is made difficult by the occasional connection of both.

One more word about the possibility of a post-mortem autolytic process. That this can be excluded I have already emphasized in my previous publication on the subject. It seems certain from the following points: first, from the direct clinical evidence with jaundice; second, from the post-mortem changes, which anatomically, show no such uniformity of distribution within a whole organ, and no such definite localization and uniformity of cellular destruction and fatty metamorphosis, unless they are caused by an additional, rapid post-mortem bacterial invasion, as for instance, by the bacterium coli, which, however, could be excluded in these cases; third, the lesion has been found the same in the autopsy of one of the cases, in which it was suspected during life by Dr. Symmers, then house physician at the City Hospital, and which we were fortunate enough to do almost immediately after death.

It is plain that the lesion presented can not be termed a hepatitis; the term "necrotic cyanotic liver with jaundice" (*hepar cyanoticum necroticum cum ictero*) appears best to describe it.

## A CASE OF TRICHINOSIS: TRICHINELLA FOUND IN BLOOD TAKEN FROM AN ORDINARY EAR PUNCTURE

GROSVENOR CROSS, M.D.

MINNEAPOLIS

In April, 1909, Herrick and Janeway<sup>1</sup> reported the finding of trichinellæ in the blood taken from the arm veins of a patient suffering from trichinosis. At the first trial four embryos were found in 10 c.c. of blood; a subsequent specimen of 1.5 c.c. from the same patient showed two trichinellæ, which were found without protracted search. An excellent



Trichinella found in blood taken from an ordinary ear puncture.

photomicrograph is reproduced in their article. Attempts to find embryos in blood taken from the veins of three other individuals of the same family with clinical trichinosis were unsuccessful.

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1. Herrick, W. W., and Janeway, T. C.: Demonstration of the *Trichinella Spiralis* in the Circulating Blood in Man, *THE ARCHIVES INT. MED.*, 1909, iii, 253.

In May, 1910, Mercur and Barach<sup>2</sup> reported the finding of two trichina embryos in 10 c.c. of blood taken from the median cephalic vein, following the method of Staübli.

Herrick and Janeway's cases occurred in March, 1909; Mercur and Barach's in January, 1910. In the article of Herrick and Janeway, the finding of trichina embryos in blood taken from the finger was suggested as a possible means of diagnosis, but, as far as I have been able to discover, no case has been reported in which such a procedure has resulted successfully. I therefore wish to present the following case, which was reported to the Minnesota Academy of Medicine in February, 1910:

The patient had been ill since August 17, 1909. On the 24th a diagnosis of trichinosis was made on the basis of edema of the face, together with a differential count, showing 9,100 white cells and 20 per cent. of eosinophils. On August 20 the white cells numbered 10,100, eosinophils 38 per cent. On August 27 the white cells numbered 11,200, with 44 per cent. eosinophils. On the 25th and 26th the stools were examined carefully for trichinae, but none were found. Excision of a piece of muscle for examination could not be done, and on the 25th it was determined to examine the blood for parasites and preparations were made to take a quantity of blood from a vein; it was not feasible, however, to get a needle into a vein, and, as an experiment, an ordinary puncture was made in the lobe of the ear and 1 c.c. of blood squeezed out by continued effort; this was laked with 12 c.c. of 3 per cent. acetic acid, centrifuged, and the sediment examined under low power. The trichinella reproduced with this report was easily found, and two others which were not quite so clearly marked. The photomicrograph was made by Dr. W. M. Chowning. Repeated examinations of the blood, on succeeding days, failed to show any further organisms.

It is worthy of note that the parasite reproduced herewith was found in this patient's blood on the eighth day after his first clinical symptom, and that no others were found later. Just as in Herrick and Janeway's cases, we were unable to discover parasites in the stools.

No attempt was made to obtain blood directly from a vein, and the fact that a comparatively small amount of blood, taken from a diagnostic puncture of the skin, showed these three trichinellae, suggests that possibly it may be easier to obtain the parasites in the mixed arterial and venous blood than in the blood which has traversed the capillaries and is taken only from the veins.

Nicollet and Seventh Streets.

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2. Mercur, W. H., and Barach, J.: A Case of Trichinosis, with Recovery of Parasite from the Blood and Muscle, *THE ARCHIVES INT. MED.*, 1910, v. 530.



## THE PREVALENCE OF HOOKWORM INFECTION IN THE BETTER CLASS OF SOUTHERN WHITE PEOPLE

J. G. GAGE, M.D., AND C. C. BASS, M.D.  
NEW ORLEANS

We offer the results of this investigation as an indication of the prevalence of hookworm and other worm infections among the better class of people in the South. Statistics are at hand showing the prevalence among army recruits, hospital patients, laborers and the poorer class, but statistics showing the prevalence of the disease among the upper classes are wanting. Recently Winthrop examined sixty-six students in the Mobile Medical College, of whom thirty-three, or 50 per cent., were found infected.

Dr. Dock suggested the examination of the students of Tulane University because the results might serve as an index of the prevalence among apparently healthy individuals representing a large area of the South.

The total number of students examined was three hundred and fifteen. Of this number one hundred and four, or 33 per cent., harbored intestinal parasites; seventy-nine, or 25 per cent., were infected with hookworms. There were also nineteen cases of infection with *Trichocephalus*, five *Strongyloides*, five *Hymenolepis nana*, and one *Tania saginata*. We were unable to separate students residing in cities from those residing in the country and smaller towns, except in the case of New Orleans students. Of two hundred and fifty-nine students not residents of New Orleans seventy-eight, or 30.1 per cent., were infected with hookworm.

Table 1 gives the results by states. New Orleans students are classed separately. Students who had lived in the country or small towns when children and had since moved to New Orleans are not classed as New Orleans students.

From this table it is seen that a large proportion of the students from Louisiana, Mississippi, Alabama, Georgia, Texas and Arkansas were infected with hookworms. The other southern states have such a small representation that the negative findings carry little weight.

Many students, on hearing that others from their towns or states were infected, took a course of thymol on their own responsibility without first having their stools examined. Some of these gained weight after-

ward, several as much as ten or fifteen pounds. Some of them, no doubt, would have shown infection if the examination had been made before they took thymol.

Double infections were not frequent, only six being found: three with hookworm and trichocephalus, one with trichocephalus and hymenolepis, one with hookworm, hymenolepis and strongyloides and one with hookworm and *Tania saginata*.

For most of the work slides 2 by 3 were used, the spreads covering as much of the slide as was convenient to handle and examined with a low power objective without cover-glasses. From one to four such prepa-

TABLE 1.—INTESTINAL INFECTION AMONG STUDENTS AT TULANE UNIVERSITY, BY STATES

States.	Total.	Negative.	Hookworm.	Trichocephalus.	Strongyloides Intest.	Hymenolepis Nana.	Tania Sag.	Double Infection.
Louisiana .....	86	47	27	10	2	3	..	(1-2) (2-4) (1-3-4)
New Orleans .....	47	47	1	4	1	1	1	.....
Mississippi .....	55	38	14	1	1	1	..	.....
Alabama .....	34	19	14	1	..	..	..	.....
Georgia .....	14	7	7	..	..	..	..	.....
Texas .....	24	17	7	1	..	..	..	.....
Arkansas .....	13	9	4	..	..	..	..	.....
Tennessee .....	10	6	2	1	1	..	..	.....
Oklahoma .....	4	3	1	..	..	..	..	.....
Florida .....	55	4	1	..	..	..	..	.....
South Carolina .....	2	2	..	..	..	..	..	.....
Kentucky .....	1	1	..	..	..	..	..	.....
Missouri .....	3	3	..	..	..	..	..	.....
Illinois .....	2	2	..	..	..	..	..	.....
Pennsylvania .....	1	1	..	..	..	..	..	.....
Massachusetts .....	1	1	..	..	..	..	..	.....
Canada .....	1	1	..	..	..	..	..	.....
Mexico .....	2	2	..	..	..	..	..	.....
Porto Rico .....	1	..	1	1	..	..	..	(1-2)
Roumania .....	1	1	..	..	..	..	..	.....
Total .....	315	211	79	19	5	5	1	4

rations were carefully examined. In ninety-two of the specimens five ordinary 1 by 3 slide preparations were examined by each of five different men. By this method hookworm eggs were found in forty-one specimens. All specimens negative by this method were examined by the special method described<sup>1</sup> by one of us. Of two hundred and seventy-four specimens which were negative by the ordinary method of examination, thirty-eight, or 13.8 per cent., showed hookworm eggs by this method.

1. Bass, C. C.: Some of the Difficulties in the Diagnosis of Mild Hookworm Infection, Louisville Month. Jour. Med. and Surg., 1910, xvi, 277.

Of the ninety-two specimens in which twenty-five slides of each were examined, twenty-four were found to contain ova. When the negative specimens were properly centrifuged and examined eight others were found infected. Therefore 25 per cent. of the positive cases were missed by the examination of twenty-five slides by the ordinary method. Table 2 gives the results by both methods:

TABLE 2.—RESULTS OF PARALLEL STOOL EXAMINATIONS BY TWO METHODS.

Method.	Hookworm.	Trichocephalus.	Strongyloides intestinalis.	Hymenolepis nana.	Tenia saginata.
Ordinary method.....	41	3	4	3	..
Bass' method, cases missed before.....	38	16	1	2	1

It is evident that many mild infections are overlooked in the ordinary method of stool examination, since about one-half of our series were found by the special method. We have come to the conclusion, however, that for ordinary purposes the calcium chlorid solutions as described by Bass<sup>2</sup> are unnecessary. Washing with water alone is sufficient unless one wishes to get the eggs as free from debris as possible, when the calcium chlorid solutions are very useful.

Only four of forty-seven of the infected students whose history was obtained on this point gave a negative history as to ground-itch. Six others were not sure; the rest gave a positive history of ground-itch from six months to fifteen years before. The majority of non-infected students also gave a positive history; exact figures are wanting, but those giving a negative history were few.

No student examined considered himself ill, and very few of those infected with hookworm presented symptoms. However, it occurred so often that it became the rule that when the investigation was started on a new class or department, very few of the first to present themselves for examination were infected, but of those from whom it was difficult to get specimens for examination, either because they were sure they were not infected or were not interested enough to find out, a much larger proportion were infected.

Table 3 shows the comparative blood findings in sixty-six of the cases.

2. Bass, C. C.: Mild Uncinaria Infections, THE ARCHIVES INT. MED., 1909, iii, 446.

The hemoglobin estimations were made with a Tallqvist scale. In making the differential counts 200 to 500 cells were counted.

From Table 3 it is evident that the blood-picture is not greatly affected in mild infections. The hemoglobin in non-infected students was but slightly higher than in infected ones. Although the average eosinophil count was somewhat higher in the infected than in the non-infected students, the eosinophils were not increased at all in many who harbored the parasites. In one spread counted, not one eosinophil was seen in counting 500 cells; some spreads from non-infected students showed from 4 to 8 per cent. and one 17 per cent. So while the presence of an eosinophilia should lead us to examine the stools, its absence should not influence us to neglect it.

TABLE 3.—COMPARATIVE BLOOD FINDINGS IN SIXTY-SIX CASES OF INTESTINAL INFECTION

Estimation.	Negatives.			Hookworm.			Trichuria.			Strongy- loides intestinalis			Hymen- olepis nana.		
	Highest.	Lowest.	Average.	Highest.	Lowest.	Average.	Highest.	Lowest.	Average.	Highest.	Lowest.	Average.	Highest.	Lowest.	Average.
Hemoglobin .....	100	80	95	100	80	92	90	85	87.5	90	80	84	90	85	89
Eosinophils .....	9.4	0.0	1.9	21.0	0.0	5.0	5.0	1.0	3.1	13.2	2.5	8.9	7.0	1.6	4.6

The above results demonstrate that hookworm infection is prevalent not only among the working classes and poor people, but also among the upper classes in infected districts; that in the country and smaller towns at least 30 per cent. of young adults between the ages of 15 and 25 are infected. Judging from the number who give a history of ground itch, a much larger proportion of people under this age harbor the parasite.

We wish to emphasize the value of the washing and centrifugalizing method of examination in detecting mild infections. Our results would indicate that two-thirds of the mild infections are overlooked in the ordinary stool examination.

We wish to thank Dr. W. C. Harkey, of Kansas City, Mo., for his assistance in part of this work.

## A PRELIMINARY REPORT ON THE DIAGNOSTIC VALUE OF THE INTRACUTANEOUS TUBERCULIN TEST

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Within the last few years the demand for diagnostic signs that will permit of early diagnosis in all forms of tuberculosis has caused considerable interest in the application of various tuberculin tests. The difficulties in the way of the proper application of the subcutaneous test and its subsequent proper observation, together with its inapplicability in febrile cases, has brought forth various cutaneous tests, the two of most importance being the conjunctival test of Wolff-Eisner and the cutaneous test shortly afterward announced by von Pirquet.

Modern literature on tuberculosis abounds with contributions on this subject. In spite of this, the medical mind is to-day in a state of confusion as to the interpretation of these reactions; and, as a result, they are popularly used as short cuts to diagnosis, the result of reactions is frequently misinterpreted, and an importance attributed to them which leads to the neglect of painstaking physical examination of the patient, with results too often disastrous to his welfare.

Recently, Mantoux and Roux,<sup>1</sup> in France, and Römer and Mendel,<sup>2</sup> in Germany, have called attention to another tuberculin test, namely, the intracutaneous tuberculin reaction. The technic of this test is briefly as follows:

With a hypodermic syringe armed with a fine needle, one injects into the upper layers of the cutis, preferably in the upper part of the back, a minimum amount of a 1-to-5,000 solution of old tuberculin (1/100 mg.). A very small wheal about the size of the head of a pin is thus produced. The absence of this wheal indicates that the fluid has been injected too deeply. The reaction, if positive, is of extreme exactness. It appears within a few hours in the form of infiltration, merely palpable or already visible of red or white color. After twenty-four hours, the infiltration has increased, is pink or light red, and occasionally edematous with an

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1. Mantoux and Roux: München. med. Wehnschr., 1908, lv, 2117.

2. Römer and Mendel: Beitr. z. Klin. d. Tuberc., 1909, xiii, 139.

erythematous zone surrounding it. After the lapse of forty-eight hours, the reaction has reached its climax. The central papule and peripheral area have become more intense, and occasionally, the two areas are separated by an intermediate zone which makes the picture even more characteristic. The extent of the infiltration is seldom less than the size of a ten-cent piece, and often more than that of a fifty-cent piece. With the peripheral area included, it may attain the size of the surface of a hand. In some cases, the infiltration appears with a porcelain-white center and a decidedly reddened area around it. After forty-eight hours, the reaction gradually decreases, though it is frequently visible for a long time as a pigmented, dark-red colored spot, with sometimes a branny scaling of the skin. There is neither febrile nor general reaction. A pseudoreaction produced by trauma may be mistaken for a true reaction. This pseudoreaction will invariably have disappeared before forty-eight hours have elapsed.

Considerable diagnostic value has been attached to this test by the above-named authors. In recent elaborate experiments with cattle Römer and Joseph<sup>3</sup> have observed a remarkable parallelism between the intracutaneous test and the subcutaneous injections, in that all animals which reacted strongly to the intracutaneous test, also reacted subcutaneously, as did also those which reacted weakly to the intracutaneous test. Conversely, the majority of those failing to react to the intracutaneous test, also remained reactionless to the subcutaneous injection.

Attention has been called by Römer and Joseph to the greater delicacy of this test over those applied to the conjunctiva and to the skin. This claim must rest on sound theoretical ground, when we take into consideration the unreliability of cutaneous and conjunctival reactions because of faulty technic. Particularly is this true in the cutaneous test. In the attempt to apply the test we have repeatedly examined non-tuberculous patients in whom a previous diagnosis of tuberculosis had been made because of a trauma produced by deep scarifications of the skin. It frequently happens that extensive denudations of the skin allow the absorption of quantities of tuberculin sufficient to produce reactions in healthy people who are carriers of inactive tuberculosis. Von Balen,<sup>4</sup> in an article in the last number of the *Beiträge zur Klinik der Tuberculose*, has given emphasis to Virchow's epigram, "Wir sind alle am Ende ein bisschen tuberculös," by calling attention to the fact that the interpretation of the significance of the tuberculin reaction must depend on the result of the application of very small doses. That the vast majority of

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3. Römer and Joseph: *Beitr. z. Klin. d. Tuberc.*, 1909, xiv, 1.

4. von Balen: *Beitr. z. Klin. d. Tuberc.*, 1910, xv, 175.

TABLE I

Name.	Age.	Clinical Diagnosis.	Test		Remarks.
			Cutaneous.	Intra-cutaneous.	
Mrs. B. ....	29	Pulmonary tuberculosis.	+	+	Bacilli absent.
Michael A. ....	19	Pulmonary tuberculosis.	+	+	Bacilli absent.
Karl D. ....	38	Pulmonary tuberculosis.	-	-	bled later of hemoptysis.
Margt. O'H. ....	...	Pulmonary tuberculosis.	+	+	Bacilli absent.
James O'H. ....	...	Pulmonary tuberculosis.	+	+	Bacilli absent.
Edw. H. ....	38	Pulmonary tuberculosis (arrested).	-	-	Bacilli absent.
Eddie H. ....	5	Intestinal hepatitis.	+	+	
Geraldine C. ....	4	Pulmonary tuberculosis.	+	+	Bacilli absent.
Mary S. ....	8	Pulmonary tuberculosis.	+	+	Mother has open tuberculosis.
Angelina W. ....	2 1/2	Pulmonary tuberculosis.	+	+	Bacilli absent.
James C. ....	4 1/2	Pulmonary tuberculosis.	+	+	has syphilis.
E. R. ....	22	Pulmonary tuberculosis.	+	+	Husband has open tuberculosis.
Mrs. McM. ....	26	Pulmonary tuberculosis.	+	+	Sister has open tuberculosis.
John F. ....	6	Tuberculous adenitis.	+	+	Adenoid and tonsils removed one year ago.
Alfio B. ....	9	Tuberculous adenitis.	+	+	Enlarged tonsils and adenoid.
Catherine O'H. ....	4	Tuberculous adenitis.	+	+	Parents have pulmonary tuberculosis.
Paul D. ....	12	Enlarged tonsils and adenoid.	+	+	Brother has open tuberculosis.
Mary M. ....	12	Enlarged tonsils and adenoid.	+	+	Brother has open tuberculosis.
James M. ....	11	Enlarged tonsils and adenoid.	+	+	Father has open tuberculosis.
Zola C. ....	4	Enlarged tonsils and adenoid.	+	+	Father and sister have pulmonary tuberculosis.
Vera C. ....	3	Enlarged tonsils and adenoid.	+	+	Father and sister have pulmonary tuberculosis.
Annie O'H. ....	15	Enlarged tonsils.	+	+	Parents have pulmonary tuberculosis.
Mrs. D. ....	41	Negative.	-	-	Son has open tuberculosis.
Mrs. F. ....	37	Negative.	-	-	Daughter has open tuberculosis.
Mrs. M. ....	31	Negative.	-	-	Husband has open tuberculosis.
James O'H. Jr. ....	11	Negative.	-	-	Parents have pulmonary tuberculosis.
Allice A. ....	12	Negative.	-	-	Tuberculosis in family.
Pauline W. ....	14	Negative.	-	-	Mother has open tuberculosis.
Eleonor W. ....	8	Negative.	-	-	Mother has open tuberculosis.
Andrew W. ....	6	Negative.	-	-	Mother has open tuberculosis.
Edna M. ....	1 1/2	Negative.	-	-	Mother has open tuberculosis.
Annie K. ....	12	Negative.	-	-	Father has open tuberculosis.
Herbert G. ....	12	Negative.	-	-	
Nellie G. ....	12	Negative.	-	-	
Bessie L. ....	18	Negative.	-	-	
E. N. ....	26	Negative.	-	-	
S. B. K. ....	26	Negative.	-	-	
S. M. ....	1 1/2	Negative.	-	-	
G. M. ....	1 1/2	Negative.	-	-	
Edw. ....	21	Mucous colitis.	+	(?)	Cutaneous, probably trauma.

healthy adults are carriers of inactive foci of tuberculosis and will react to large doses must be generally admitted. On the other hand, in the practice of all who are observing considerable numbers of tuberculous patients, well-marked signs in the chest, and often tubercle bacilli in the sputum are frequently found in those reported as negative because the technic had allowed the applied tuberculin to be washed off by the serum rather than to be absorbed.

In view of the significance given this reaction by these investigators, we have recently applied the intracutaneous synchronously with the cutaneous test in a series of forty-two patients applying at the San Francisco Tuberculosis Clinic. Tuberculin had not been used either diagnostically or therapeutically on any of these patients, and the tests were applied at the same time in order to avoid the possibility of bringing about hypersusceptibility by a previous application, if indeed such possibility exists.

Control injections of salt solution were used in the greater number of these cases without, in any instance, a reaction arising from the control.

Of the forty-two applicants, twenty-three reacted to both the cutaneous and intracutaneous tests; ten were reactionless to both tests; nine reacted to the intracutaneous, but were reactionless to the cutaneous test; while there were none who reacted to the cutaneous and yet were reactionless to the intracutaneous. While the tests here given are insufficient in number to form a basis on which to draw definite conclusions, it would appear to indicate a delicacy of reaction in favor of the intracutaneous test.

It would be misleading in a study of this kind to draw a sharp distinction between tuberculous and non-tuberculous cases. The frequency with which tuberculosis exists, where not suspected, in the homes of those affected, has been strikingly brought forth by the results of our custom, at the Tuberculosis Clinic, of examining, wherever possible, all the members of a family in which a tuberculous patient has been found. This work has justified the probable assumption of tuberculosis in large numbers of those brought for such examination. This is not surprising when we consider the danger of infection due to the housing condition of the class who frequent free clinics. We have therefore preferred to divide our cases into (1) tuberculous, (2) non-tuberculous, and (3) persons with tuberculosis in the home. Those classified "tuberculous," were those in whom careful examination revealed definite physical signs



of active tuberculosis. The "non-tuberculous" comprised those in whom examination revealed no evidence of active disease, no suggestion of it by reason of the presence of a pathologic condition of the adenoids or tonsils, and no suggestive presence of tuberculosis in the family. In those classed as with "tuberculosis in the home" a history of prolonged and constant contact with active tuberculosis under unfavorable housing conditions, justified a special classification in order to consider intelligently the significance of tuberculin tests.

A study of the appended table will show that of the twenty-three patients reacting to both tests, ten had active pulmonary tuberculosis; three had tuberculous adenitis; in eight pulmonary tuberculosis was demonstrable in the household; while of the two classified non-tuberculous, one was sent for examination because of an obstinate cough, and the other had been pronounced tuberculous by a physician. In neither of these did the physical signs justify the diagnosis of active tuberculosis.

TABLE 2

Classification.	Total No.	Test			
		Cutaneous		Intracutaneous	
Pulmonary tuberculosis . . . . .	13	10	3	11	2
Tuberculous adenitis . . . . .	4	3	1	4	0
Tuberculosis in family . . . . .	16	8	8	13	3
Non-tuberculous . . . . .	9	2	7	4	5

Of those studied in our series, nine, or almost one-fifth, reacted to the intracutaneous but were reactionless to the cutaneous test. Of these, only one had active pulmonary tuberculosis; he also had *tuberc*, and has since died of pulmonary hemorrhage. One had tuberculous adenitis. Five of them were in tuberculous households, three of whom were children of a mother who has open tuberculosis. Of the two "non-tuberculous" of this class, one has a daughter who has tuberculous adenitis.

Almost one-fourth of our subjects (ten) were reactionless to both tests. Of these, two have pulmonary tuberculosis, one in an arrested stage who also has interstitial nephritis, and the other, a child of 4 years, has active tuberculosis. The child's father also has the disease in an active form, and two other children are delicate and have enlarged tonsils and adenoids. This entire family is representative of a type of poor resistance in which we frequently fail to obtain reactions. Five of this class were non-tuberculous; one presented himself because of severe intermittent abdominal pain which proved to be mucous colitis; one requested

examination because his sister has active tuberculosis, though the history of the sister's infection precluded the possibility of house contact; the remaining three were without interest.

This preliminary report represents a work we have just begun. The only conclusion to be drawn is the fact that it would appear that the intracutaneous test is more delicate than the cutaneous test. This is in agreement with the findings of Römer and Mendel, whose work covers a great many tests.

It is particularly desirable that a clearer interpretation of tuberculin tests should be generally acquired. Out of the confusing mass of statistics which has so rapidly accumulated, comes the conviction that the absolutely tuberculosis-free individual does not react to tuberculin. In fifty new-born infants, Schreiber obtained neither local nor general reaction, although in some instances as much as 50 mg. of tuberculin were used. Bondy in cutaneous tests on 350 new-born infants, obtained no reactions, although 71 per cent. of the mothers reacted. On the other hand, Beck, of Berlin, injected 2,137 adults without clinical evidence of tuberculosis, of whom 54 per cent. had fever reaction. Franz injected 400 soldiers with 1 to 3 mg.; of these 61 per cent. had temperature reactions.

Interpreted superficially, this great preponderance of apparently healthy adults who react tends to minimize the diagnostic value of these reactions. The smallest amount of tuberculin that can produce reactions had not been the subject of scientific investigation until the appearance of von Balen's recent communication. The value of tuberculin in diagnosis must be to differentiate the existence of active foci, producing symptoms. The individual is seldom to be found, in our opinion, who will fail to react to the enormous quantities of tuberculin absorbed in some of the cutaneous tests, which we have seen, in which large areas of skin are unnecessarily denuded. These individuals are carriers of inactive tuberculous foci. That the majority of adults are such carriers must be evident to all who have had autopsy experience in large continental hospitals. The hypersusceptibility present in the carrier of an active lesion, however, will find its clinical expression in the presence of very small doses, usually not more than 0.01 mg.

It would seem to us that we have in the intracutaneous test a method of more exact dosage than in the other method of cutaneous application. It has been our experience that the general reactions subsequent on the subcutaneous test have been avoided.

In conclusion, we would urge a more general application of this test, bearing always in mind that tuberculin tests, however applied, become a source of error when they are given a more prominent and important diagnostic place than painstaking and thorough search for physical signs.

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NOTE.—The following references also will be found of interest:

Römer: *Beitr. z. Klin. der Tuberc.*, 1909, xii, 185.

Hutinel: *Tribune méd.*, 1908, xli, 693.

Mantoux: *Presse méd.*, Paris, 1910, xviii, 10.

## HAS OVOTHERAPY, AS NOW PRACTICED, AN EXPERIMENTAL BASIS? \*

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### INTRODUCTION

Our knowledge relating to the function of the corpus luteum is limited to a few isolated and disjointed facts. The minority are based on reliable experimental data; the majority are insecurely founded on clinical observations, which permit of widely differing interpretation.

Even a cursory study of the corpus luteum under the microscope will convince an unbiased observer that a structure which is stamped with all the hallmarks of an extremely active gland must possess at least some, and probably important functions.

As Fraenkel has shown, the corpus luteum is widely distributed in the mammalian series. It should be classed among the glands of internal secretion, enjoying the unique distinction of being transitory, appearing with each cycle of rut or menstruation, and persisting during the major part of gestation.

The voluminous literature dealing with the corpus luteum is readily accessible.<sup>1</sup> In this connection only the following articles need be referred to. Fraenkel<sup>2</sup> has shown that, in most instances, the nidation of the ovum is prevented in the rabbit, if the ovary or the corpus luteum is ablated within seven days of fertilization. The doubts cast on this observation by Daels<sup>3</sup> and other investigators are based on the fact that the operation required to remove or destroy the corpora lutea may have sufficed to interrupt the pregnancy. This Fraenkel, relying on his control experiments, categorically denies. Leo Loeb<sup>4</sup> reported in 1909 that amitotic nuclear proliferation was observed in the surface epithelium of the rabbit's uterus on the fifteenth day after the formation of the corpus luteum. No such changes were noted at an earlier period (three and one-half to five and one-half days).

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\* From the Department of Pathology of Columbia University, College of Physicians and Surgeons.

1. Fellner, O.: *Med. Klin.*, 1906, ii, 1100; Villemain: *Le corps jaune considéré comme glande à sécrétion interne de l'ovaire*, Paris, 1908, Octave Doin.

2. Fraenkel: *Arch. f. Gynäk.*, 1903, lxxiii, 438.

3. Daels: *Surg., Gynec. and Obst.*, 1908, vi, 153.

4. Loeb, D.: *Arch. f. Entwicklungsmech. d. Organ.*, 1909, xxvii, 463.

Bouin and Ancel,<sup>5</sup> on the other hand (1910), assert that well-marked epithelial changes occur soon after the rupture of the ovarian follicle, and that these alterations correspond accurately in time with the development of the corpus luteum, and are summarily cut short or prevented by the removal of this body.

These few, and somewhat contradictory observations, which, here, are not reported in strictly chronological order, included practically our entire knowledge of the physiological action of the corpus luteum, until Leo Loeb<sup>6</sup> (1906-1910) in a large and most convincing series of experiments, has greatly advanced our knowledge by demonstrating that the corpus-luteum secretion "sensitizes" the uterine mucous membrane of the guinea-pig and of the rabbit in such a manner that it responds to traumatic stimuli (these may consist of the lytic action of the early ovum, or of the coarser experimental stimuli of incision) by marked proliferation of the submucosal connective tissue. Incisions into the uterus, made from two to nine days after coitus or after rut (in both cases these processes correspond to the rupture of the follicle and to the beginning formation of the corpus luteum) are followed by the appearance of multiple tumors along the line of incision. These tumors attain the size of a pea or even of a hazelnut, enlarge slowly for about ten days, and then as slowly regress. Removal of the entire ovary or of the corpus luteum prevents the appearance of the growths. The deciduomata, as Loeb denominates these transitory tumors, also develop in portions of uteri, transplanted to other parts of the body of the same animal and, though to a lesser degree, into other animals of the same species, who are in a corresponding period of rut.

Microscopically the deciduomata correspond to the maternal (decidual) part of the placenta, differing somewhat in type in the guinea-pig and in the rabbit, as should be expected from the difference of the deciduæ of these two species under normal conditions. In both, the salient features are an enormous proliferation of the connective tissue stroma, immediately beneath the epithelium and about the uterine glands. The tissues assume an exaggerated decidual character; the nuclei of the stroma enlarge and show mitoses; the cell body becomes plump and contains glycogen; the endothelial cells of the vessels enlarge and show division, and, at least in the guinea-pig, the surface epithelium contains large

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5. Bouin and Ancel: *Jour. de physiol. et path. gén.*, 1910, xii, 1.

6. Loeb, L.: The Production of Deciduomata. *Jour. Am. Med. Assn.*, 1908, 1, 1897; The Experimental Production of the Maternal Placenta, *ibid.*, 1909, lii, 1471; *Arch. f. Entwicklungs-mechn. d. Organ.*, 1909, xxvii, No. 1.

giant-cells and cell-complexes. The wider general significance of Loeb's researches cannot be entered into in this connection.

To recapitulate: Fraenkel has shown that the corpus luteum plays an important, probably an essential part, in determining the nidation of the ovum. Loeb and later Bouin and Ancel have called attention to the finer histological changes, which, under the influence of the corpus luteum, prepare the uterus for the reception of the ovum. Finally Loeb has opened a wide field, by discovering a delicate physiological method, by means of which it would seem possible to measure (perhaps even quantitatively) and to test the effect of the active corpus luteum substance.

Attempts to obtain results from the administration of corpus luteum by injection or by the oral route have been made. These experiments were, however, performed with the view of influencing metabolism or of combating the symptoms of the artificial menopause. They were performed more often on the human subject, so that no accurate observations of any local effects could be gathered. Among these studies are the work of Fraenkel, Villemin, Drevet, Lambert, Morley, etc.<sup>7</sup> Villemin alone attempted a closer pharmacological investigation of the effect of the corpus luteum substance injected intravenously.<sup>8</sup> He found that these injections produced marked circulatory depressive symptoms, and, in large doses, rapid death preceded by convulsions. He therefore concluded that corpus luteum contained two active principles, the one vasodilator in action, the other convulsant and toxic.

#### SCOPE OF THE EXPERIMENTS

In the preliminary work undertaken to devise a technic for the study of the effect of corpus luteum on metabolism, as suggested to me by Professor MacCallum, I was impressed by the lack of data relating to the local effect of corpus luteum on the uterus, and by the extreme divergence of opinion as to the gross pharmacological actions of this gland. The study of the effects on metabolism were, therefore, abandoned and the work, to be detailed below, was performed with the object of discovering:

- I. The gross pharmacological effects of the intravenous injection of extracts of corpus luteum.

- II. If corpus luteum injection can replace the normal secretion of the gland (after removal of ovaries) sufficiently (1) to produce Loeb deciduomata; (2) to bring about estrual changes; (3) to permit the con-

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7. Drevets: *Effets thérapeutiques du corps jaune*, etc., Thèse, Paris, 1907, Steinheil. Lambert: *Compt.-rend. Soc. d. biol.*, 1907, lxii, 18. Morley: *Detroit Med. Jour.*, August, 1909.

8. Lambert reports that fresh corpus luteum extract circulating through the heart of the frog causes arrest in diastole.

tinuation of pregnancy; (4) to maintain the normal condition of the uterus (i. e., avert the atrophy of castration).

III. The effect of corpus luteum injection on the hypophysis of castrated animals.

#### I. THE PHARMACOLOGICAL EFFECTS OF INTRAVENOUS INJECTION OF CORPUS LUTEUM EXTRACT

The gross pharmacological effects necessarily suggested themselves as the first step in developing a feasible technic. The corpus luteum is incontrovertibly a gland of internal secretion, if it possesses any function. Its secretion, therefore, is normally distributed by means of the blood vessels, though possibly absorption might be effected through lymphatic (subcutaneous) administration, as with adrenalin, or by assimilation through the gastro-intestinal tract, similar to that obtained with thyroid substance. In view of the assertions of Villemain, it became imperative to confirm or disprove his statements.

*Experiments.*—In all experiments ether was administered for all operative procedures. Hypodermic injections, however, except in dogs, were given without anesthesia.

*Preparation of Corpus Luteum Extract.*—Dog's corpus luteum substance was obtained by shelling out the corpora from the ovary. The glands were passed through a small meat-chopper, carefully ground in a mortar with sand, and macerated at 0° C. for three hours. The extract was then freed of all coarse particles by rapid centrifugalization for from ten to twelve minutes, and used in the dilutions specified below.

Injections were made into the exposed femoral vein, care being taken to inject at an approximately uniform rate in every instance. The animal's temperature was taken before beginning the anesthesia, during the course of anesthesia, and fifteen minutes after injection.<sup>9</sup> The pulse-rate and respiration were also noted at similar intervals. Except in the first experiment, all dogs used were females..

##### I-A. INJECTIONS INTO DOGS OF DOG'S CORPUS LUTEUM EXTRACT

*Experiment 1.*—Dog, weighing 11¼ pounds; 3 gm. of substance (from 20 ovaries) in dilution of 1 to 6 (9/10 normal salt solution) injected in two equal doses at ten-minute intervals. No circulatory effect, depression of temperature of 3° (ether?). Remained permanently well.

*Experiment 2.*—Bitch, weighing 9 pounds; 11 gm. of substance in dilution of 1 to 2 injected in two doses (¾ and ¼ of whole). No effect, depression of temperature 4°. Remained permanently well.

9. As no change except a gradual fall of temperature, apparently due to the administration of ether, and proportional to the length of the narcosis, was noted, the temperature is not recorded in the later protocols. Villemain reports a rise after injection.

On account of the difficulty of obtaining material, the succeeding experiments were performed with sheep's corpus luteum, prepared as above.

#### II-A. INJECTIONS INTO DOGS OF SHEEP'S CORPUS LUTEUM EXTRACT

*Experiment 3.*—Bitch, weighing  $8\frac{3}{4}$  pounds;  $7\frac{1}{2}$  gm. substance in dilution of 1 to 2. Death immediate without convulsion; heart continued to beat for several minutes. Autopsy: The right heart was found completely blocked by solid thrombi.

*Experiment 4.*—Bitch, weighing  $9\frac{5}{8}$  pounds. Preliminary injection of 15 gm. of extract from the ovary, deprived of its corpus luteum; dilution 1 to 2. (This extract, made from the more solid portions of the ovary, was found to contain less albuminous substances (boiling) and fewer particles (microscope). No effect except marked, but transitory increase in the respiratory rate. After fifteen minutes interval, injection of 7.5 gm. of the same extract as used in Experiment 3. No effect. Killed with ether after twenty minutes. Autopsy: Numerous hemorrhagic spots found in both lungs. Histological examination showed that the hemorrhagic areas were in the course of distribution of the pulmonary artery. No cell thrombi were found. This was explained by examination of the extract in which no formed cellular elements remained after centrifugalization.

*Experiment 5.*—Bitch, weighing  $10\frac{3}{8}$  pounds; 25 c.c. of fresh dog serum was added to 25 gm. of substance in dilution of 1 to 1, and after fifteen minutes injected in two doses of 20 c.c. and 10 c.c. (corresponding to 20 gm. of substance in dilution of 1 to 2). After the first injection, respiration was very rapid and shallow for six minutes; the second injection, fifteen minutes later, produced no effect. Killed with ether twenty minutes later. Autopsy: Fresh hemorrhagic areas in lungs.

*Experiment 6.*—Bitch, weighing 16 pounds; 32 gm. substance, dilution 1 to 1. This extract was preserved at  $0^{\circ}$  for twenty hours instead of three hours. Injection of 8 c.c. produced stoppage of respiration for two minutes; heart slow and feeble; after five minutes a convulsion, then slow recovery. Ten minutes after the first injection, 20 c.c. more were given, heart action very feeble, irregular and slow. Ten minutes later 5 c.c. were given. Gradual recovery. Killed with ether after fifteen minutes. Autopsy: Lungs normal; firm clot almost completely blocking the auriculoventricular opening and extending into the inferior vena cava.

In order to exclude operative intervention rabbits were used for the succeeding experiments. Injections were made into the ear vein. The extracts were from twelve to twenty-four hours old. In the hirudin experiments to be detailed, equal parts of the same extract were employed in hirudinized and control animals. The rabbits weighed from 1,500 to 2,000 gm. and all were females.

#### II-B. INJECTION INTO RABBITS OF SHEEP'S CORPUS LUTEUM EXTRACT

*Experiment 7.*—Injection of 6 c.c. of extract 1 to 1; immediate death in convulsion.

*Experiment 8.*—Preliminary injection intravenously of 0.5 gm. of hirudin in salt solution. After two minutes 6 c.c. of extract 1 to 1. No effect, remained permanently well.



*Experiment 9.*—Repetition of Experiment 8 in a second animal. Same result.

*Experiment 10.*—Injection of 2 c.c. extract 1 to 1; no effect. Same extract twenty-four hours later, 2 c.c. Immediate death with convulsion.

*Experiment 11.*—Injection of 1 c.c. 1 to 1; death in five minutes.

*Experiment 12.*—Injection of 1 c.c. 1 to 1; convulsions; died in ten minutes.

*Experiment 13.*—Injection of 6 c.c. of ovarian extract 1 to 1. After fifteen minutes slight opisthotonos, then permanent recovery.

*Epicritical Remarks.*—The results obtained in the above thirteen experiments conclusively prove that Villemin's deductions are entirely erroneous. The two dogs in whom an homologous extract was used, suffered no ill effect.<sup>10</sup>

The four dogs injected with heterologous (sheep's) extract, reacted in different ways: these differences depending on controllable factors. In Dog 3 it was found that approximately 0.15 to 1 c.c. of extract to the pound of body weight produced immediate death. Autopsy showed that death was due to right heart thrombi.

Dog 4 received a preliminary injection of ovarian extract, which prepared from less glandular elements, produced a minor degree of thrombosis, and temporarily reduced the coagulability of the blood.

The succeeding dose of corpus luteum extract, which was sufficient to kill Dog 3 was, therefore, borne without ill effect. Autopsy in this case demonstrated that, as the coagula were slower in formation, and less in degree, the thrombosis did not take place in the heart, but in the branches of the pulmonary artery.

A similar protective action to the lethal dose was obtained in a different way (Dog 5) by partly neutralizing or inhibiting the coagulant effect of the extract by means of addition of fresh dog's serum *in vitro* before injection. Autopsy again showed lesions in the lungs.

In Dog 6 it was hoped to weaken the extract by allowing it to age (twenty hours instead of three hours). The first injection of 8 c.c. was, however, perilously close to the fatal dose. Great cardiac weakness and convulsions supervened, but the dog nevertheless recovered. The dog then bore 25 c.c. in addition, with but slight effects. The first dose had reduced the coagulability to such a degree that double the usual fatal amount was borne without difficulty. Autopsy made evident that thrombi had almost completely blocked the tricuspid opening and the cava, but, through some favorable accidental mechanical factors, the circulation was yet able to continue.

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<sup>10</sup> In Experiment 1, the great dilution of 1 to 6 accounts for the negative result. In Experiment 2 transient acceleration of respiration was noted. The dog was allowed to live in order to determine whether remoter effects would develop. Had the dog been killed, pulmonary emboli, doubtless, would have been found.

In the rabbits it was found that from 1 to at most 2 c.c. was the fatal dose (in Rabbit 10, although 2 c.c. failed to kill on the first day, yet 2 c.c. of the same extract, twenty-four hours later, produced immediate death).

By giving a preceding injection of hirudin (purified leech extract), which completely inhibits the coagulability of the blood for several hours, three times the fatal dose was found to produce no ill result. In all the rabbits that died, solid thrombi filled the right auricle and ventricle.

*Deductions Based on the Experimental Findings.*—The results obtained by Villemain are, therefore, to be interpreted as due to intravascular thrombosis and not to either a vasodilator or general toxic action. Neither flushing of the peripheral parts nor increased peristalsis, as described by this author, were noted in my series in any instance.

A word of caution to investigators who employ the intravascular route for administration of tissue extracts may be permitted. Naunyn and Rauschenbach<sup>11</sup> have shown that coagulating substances can be obtained from any and all cells. Such substances as thrombokinase or those acting similarly are closely bound to the protoplasm. Consequently, when more minute and complete subdivision of cells is obtained, more of these thrombogenic substances are set free. On the other hand, larger aggregations of cells produce thrombosis through their action as foreign bodies, rather than through the ferments set free. Veit and his pupils largely based their placental toxin theory on the convulsion produced by intravascular injections of placental extracts. It has required the combined efforts of many investigators—Lichtenstein, Mathes, Schenk, etc.,<sup>12</sup> employing the methods used in my investigation, to undermine and, let us hope, to lay permanently at rest these misleading conclusions.

The results of intravascular injections of corpus luteum extract, in massive doses, produce intravascular coagulation without any well-marked pharmacological effect.

## II. CAN CORPUS LUTEUM INJECTIONS REPLACE THE NORMAL SECRETION OF THE GLAND?

The preliminary investigation demonstrated that intravenous administration of corpus luteum could not be performed with safety. Throughout the rest of the experiments subcutaneous injection, or administration by mouth, or a combination of the two were employed.

11. Naunyn: Arch. f. exper. Path., 1873, i, 1. Rauschenbach: Ueber die Wechselwirkung zwischen Protoplasma und Blutplasma, Inauguration Diss., Dorpat, 1883. Loeb, L.: Med. News, 1905, lxxxvi, 577.

12. Lichtenstein: Zentralbl. f. Gynäk., 1909, xxxiii, 1313; Arch. f. Gynäk., 1908, lxxxvi. Mathes: Zentralbl. f. Gynäk., 1908, xxxii, 1548. Schenk: Zentralbl. f. Gynäk., 1909, xxxiii, 1500.

As Loeb has definitely shown that in the guinea-pig and rabbit the uterine mucosa reacts in a well-defined and easily recognizable manner to the chemical action of the corpus luteum, these animals were chosen for my experiments. The work of Bouin and Ancel did not appear until after most of the experiments had been concluded. Nevertheless, all the sections were reexamined with a view of determining whether or not the histological changes, described by these authors, were present.

As the technic throughout was identical, and variations were limited to the interval between double oöphorectomy and incision of the uterus, and to the quantities of corpus luteum extract injected and the route of administration, I am able to summarize the results most briefly.

#### METHODS EMPLOYED

*Extract.*—All the extracts were obtained from the fresh corpora lutea of sows. The ovaries were dipped for an instant into 4 per cent. liquor formaldehydi and then rapidly washed in two changes of sterile water to eliminate surface bacteria. The remaining steps were identical with those described in connection with the previous series, except that asepsis was more rigidly observed. The amount of normal salt solution used was 1 to 1 by weight. Fresh extracts were prepared every seventy-two hours, so that the extracts actually injected were twelve, twenty-four, thirty-six, forty-eight, sixty and seventy-two hours old; then the series was begun again.

*Method of Administration.*—For hypodermic use extracts were centrifuged for five minutes; for mouth administration the unclarified extracts were used. The site of injection preferably was the back. In a few instances some induration resulted; in one case an abscess developed. In the great majority of experiments the fluid was absorbed rapidly and completely. The extract, when injected subcutaneously, was diluted with an equal quantity of salt solution. Quantities of extracts, as given in the protocols, are based on the amount of solid substance from which the extract was prepared.

*Operative Procedure.*—The technic employed was that of Loeb. Dr. Loeb very kindly demonstrated his methods to me and permitted me to examine his specimens. In addition, he offered many practical suggestions and cautions which proved invaluable. The ovaries were removed through the lumbar route. This operation can be performed without shock or interference with the uterus, in from eight to fifteen minutes. Incisions of the uterus were made through a median abdominal incision. A part of each horn of the uterus was split along its anterior surface and numerous transverse cuts made in addition.

The rabbits survived these two procedures without trouble. Numerous guinea-pigs, however, were lost. The following is a brief summary of the protocols of the animals which survived sufficiently long to prove of value:

#### EXPERIMENTS ON RABBITS

*Experiment 14.*—Double oöphorectomy and incision of uterus at one operation. Injections of 0.5 gm. every twenty-four hours begun on eighth day. Died eight days later (sixteen days after operation). Two masses, respectively, the size of small and large pea at autopsy.

*Experiment 15.*—Same as 14, except that 1 gm. was given every twenty-four hours. Killed on sixth day (fourteen days after operation). Everted mucosa forming small rosettes.

*Experiment 16.*—Double oöphorectomy; 2 gm. by mouth twice daily throughout; incision of uterus on fifth day. Killed six days after second operation. Bright red nodular masses.

*Experiment 17.*—Same as 16, except that 1 gm. was given twice daily and that the animal was killed on the twelfth day after the second operation. The uterine incision showed much everted hypertrophied mucosa.

*Experiment 18.*—Double oöphorectomy (large corpora lutea); 1 gm. by hypodermic injection, mornings, and 1 gm. by mouth, evenings, throughout. Incision of uterus on the fifth day. Died on eighth day after second operation. Nodules along line of incision.

*Experiment 19.*—Same as 18, except that 0.5 gm. was given by hypodermic injection and 1 gm. by mouth. Died on tenth day after second operation.

*Experiment 20.*—Double oöphorectomy (large corpora lutea); incision of uterus on fifth day. Killed nine days after second operation. No injections. Used as control.

#### EXPERIMENTS ON GUINEA-PIGS

*Experiment 21.*—Double oöphorectomy and incision of left horn (in right horn three pregnancies of fifteen days); 0.5 gm. by hypodermic injection; killed tenth day. No nodules left horn. Pregnancies nearly absorbed.

*Experiment 22.*—Double oöphorectomy; 0.5 gm. by hypodermic injection; 1 gm. by mouth. Aborted on fourth day.

*Experiment 23.*—Double oöphorectomy; 0.5 gm. by hypodermic injection; 1 gm. by mouth. Aborted seventh day.

*Experiment 24.*—Double oöphorectomy and incision of uterus; 1 gm. hypodermic injection; killed ninth day. No nodules.

*Experiment 25.*—Double oöphorectomy; 1 gm. by hypodermic injection every day. Incision of uterus sixth day. Died next day.

*Experiment 26.*—Double oöphorectomy; 1 gm. by hypodermic injection every day. Incision of uterus seventh day. Died next day.

*Experiment 27.*—Double oöphorectomy; 1 gm. by hypodermic injection for five days. Incision of uterus fifth day; 0.5 gm. by hypodermic injection thereafter. Killed ten days later. No nodules.

*Experiment 28.*—Double oöphorectomy; 2 gm. by mouth twice daily. Died from anesthetic fifth day.

*Experiment 29.*—Double oöphorectomy; 0.5 gm. by mouth twice daily. Incision of uterus fifth day. Died four days later. No nodules.

*Experiment 30.*—Double oöphorectomy; 2 gm. by mouth twice daily throughout. Incision of uterus fifth day. Killed ten days later. No nodules.

*Experiment 31.*—Double oöphorectomy; 0.5 gm. by hypodermic injection; 2 gm. mouth daily throughout. Incision of uterus fourth day. Killed twelve days later. No nodules.

*Experiment 32.*—Double oöphorectomy; 0.5 gm. by hypodermic injection, 1 gm. by mouth daily throughout. Incision of uterus seventh day. Died five days later. No nodules.

*Experiment 33.*—Double oöphorectomy; 0.5 gm. by hypodermic injection; 0.5 gm. by mouth daily throughout. Incision of uterus ninth day. Died two and one-half days later. Numerous small nodules.

*Experiment 34.*—Double oöphorectomy; incision of uterus eighth day. Killed six days later. Control.

*Experiment 35.*—Double oöphorectomy: incision of uterus fifth day. Killed seven days later. Control.

*Experiment 36.*—Double oöphorectomy: incision of uterus fifth day. Killed ten days later. Control.

#### HISTOLOGICAL EXAMINATIONS

All suspicious nodules in the line of incision, and a portion of the uterus above and below the operation wound were examined. On the average five blocks from each case were cut in serial section and stained with hematoxylin and eosin.

*Results in Regard to Deciduomata of Loeb.*—Loeb has shown that, in response to appropriate stimuli, deciduomata appear in the guinea-pig and rabbit from two to nine days after the formation of the corpus luteum.

As injections might not correspond to Nature's efforts, variations of time, dosage and method of administration were employed. Experiments 14 to 19 and 24, 27, 29, 30, 31, 32 and 33 can be utilized in this connection.

Although, particularly in the rabbits, and in guinea-pigs 21 and 23, macroscopic nodules were present, deciduomata according to Loeb's histological criteria were uniformly absent.

*Results in Regard to the Estrual Cycle.*—As previously noted certain changes occur in the surface epithelium of the rabbit's uterus (probably also in that of the guinea-pig) during the interval between each period of rut. Loeb found such changes—amitotic nuclear proliferation—about the fifteenth day, not on the third or fifth day. Bouin and Ancel assert that both macroscopic and microscopic alterations can be observed within forty-eight hours of a non-fecundating coitus (male with vasa deferentia ligated), and that these changes increase progressively until the fourteenth day. They report that the nuclei form columns and that the cytoplasm appears as undivided symplasmatic sheets. Removal of the corpus luteum produces rapid regression at any stage.

Without entering into any discussion of the discrepancies observable between these views, I may state that, in the uteri of neither the rabbits nor the guinea-pigs of my series were any nuclear proliferations noted.

*Results in Regard to Continuation of Pregnancy after Castration.*—Fraenkel and others have asserted that castration or extirpation of the corpus luteum, early in pregnancy, produced absorption of the ovum. Considerable doubt has been cast on these observations.\* Whether the continuation of pregnancy depends on the formation of the maternal

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\* Loeb and Hunter: (Univ. Penn. Med. Bull., 1908, x, 294) found that removal of the mammary gland frequently produced absorption of the pregnancies or abortion in guinea-pigs.

decidua (as shown by Loeb), and whether this structure is essential for nutritional purposes, I am unable to state. Quite possibly, however, the decidua is merely a protective reaction against the invasive action of the trophoblast.

My experiments (21, 22 and 23) are too few and incomplete to add anything to our knowledge. In Experiment 21 the operative interventions were sufficiently extensive to account for the absorption of the pregnancies. In Experiments 22 and 23 abortion occurred on the fourth and seventh day after operation. The injection of extract certainly did not produce any increased stimulus toward a continuation of pregnancy.

*Results in Regard to Castration Atrophy.*—It is well known that castration is followed by atrophy of the uterus. The statements regarding the rapidity of this process vary somewhat. Fraenkel says that fourteen days after castration the rabbit's uterus is a narrow, flaccid yellowish band. The muscle layer has atrophied to such an extent that the thickness of the mucous membrane exceeds it. Bouin and Ancel state that the atrophy is rapid.

In order to be in a position to determine this point in my experiments, controls were essential. For comparison I chose Rabbits 18 and 20, the ovaries of both containing well-developed corpora lutea. Guinea-pigs 31 and 36 afforded a similar contrast. The ovaries of Guinea-pigs 27, 30 and 34 contained no corpora lutea. Guinea-pigs 32 and 35 were also of value in this connection. In addition all the other uteri were studied in order to determine whether atrophy was progressive and proportional to the time elapsed since castration, and whether the injections had any recognizable influence upon involution.

The observations extend only over a period from five to seventeen days after oöphorectomy. Both mucosa and muscle layer appeared normal. Possibly the nuclei of the epithelial cells were somewhat narrower than in non-castrated animals, but no distinct histological evidence of atrophy was observed in either the injected or control animals within seventeen days of castration.

### III. THE EFFECT OF CORPUS LUTEUM INJECTION ON THE HYPOPHYSIS OF CASTRATED ANIMALS

The interaction and interdependence of the glands of internal secretion has been recognized by clinicians for some time. More recently, experimental investigators have sought to define these relationships and to discover the laws which govern their compensatory action.

For instance, absence of the thyroid gland, as in cretinism, is usually accompanied by genital hypoplasia. Acromegaly, due to tumors of the

hypophysis cerebri, is commonly followed by infantilism of the female generative glands. Adrenal tumor has been known to change the secondary female sexual characteristics into those of the opposite sex (case of Thumin<sup>13</sup>). Such observations can be indefinitely multiplied. They are of more than passing interest, but, beyond calling attention to the marvellous interaction of the organs of internal secretion, throw no light upon the subject.

Even in normal pregnancy certain symptoms, such as coarsening of the face, growth of hair, etc., point to hypophyseal hyperactivity. Erdheim and Stumme,<sup>14</sup> in a thorough anatomical study, have shown that during pregnancy the hypophysis enlarges and undergoes characteristic morphological changes.<sup>15</sup> In order to make these clear, it will be necessary to enumerate briefly the histological constituents of the gland.

The hypophysis is composed of three parts, the posterior or nervous portion, with which we may include the infundibulum, the pars intermedia, or *Epithelialsaum* and the anterior lobe, which is glandular. The nervous portion of the hypophysis does not concern us here. As physiologists have shown, its extracts have a strong pressor (vasoconstrictor) influence, similar to adrenalin, and, according to some, the extract acts as a powerful oxytotic (Bell<sup>16</sup>). The pars intermedia varies in different species, and is of interest largely because within it may be found glandular spaces, which resemble thyroid acini, and contain colloid within their lumen.

The anterior lobe chiefly engages our attention. It is composed of closely packed groups of cells, so arranged that nearly every individual cell is in direct contact with the walls of one or more capillaries. Three varieties of cells have been described. Quite probably, all three express merely different stages of function or metabolic activity. This classification is based upon the staining properties of the cells. Acidophil (eosinophil) cells under ordinary conditions predominate in number; basophil (staining with hematoxylin, etc.) are numerically second, and a smaller number of chromophobe cells (whose protoplasm is indifferent to both acid and basic dyes) are also present. For details, the reader is referred to Erdheim and Stumme, and to an excellent morphological study of the hypophysis in mammals, by Trautmann.<sup>17</sup> A complete review of the

13. Thumin: Berl. klin. Wchnschr., 1909, xlii, 103.

14. Erdheim and Stumme: Beitr. z. path. Anat. u. z. allg. Path., 1910, xlii, 1.

15. Comte: Beitr. z. path. Anat. u. z. allg. Path., 1898, xxiii, 90. Launois, P. E., and Mulon, P.: Etude sur l'hypophyse humaine à la fin de gestation. Compt. rend. de l'Assn. d'anat., Nancy, 1903, v, 124.

16. Bell: Brit. Med. Jour., 1909, ii, 1609.

17. Trautmann: Arch. f. mikr. Anat., 1909, lxxiv, 311.

literature will be found in Paulesco's monograph.<sup>18</sup> Erdheim and Stumme have shown that in the course of pregnancy the basophilic cells increase enormously in number, most probably at the expense of the eosinophilic cells. It is of interest and importance to determine in response to what stimuli these changes occur.

In pregnancy we have two factors to consider in this connection. The one is the fetus and placenta, the other the persistent corpus luteum (corpus luteum of pregnancy). According to Claypon and Starling<sup>19</sup> extracts of the fetus—not of the placenta or of the uterus—produce hypertrophy of the mammary gland. Withdrawal of this influence is followed by the secretion of milk from the activated gland. This observation, solitary and unconfirmed, permits of no generalization, but draws attention to the fact that the fetal influence might also exert some power on other glandular organs, as, for instance, on the hypophysis.

In regard to the corpus luteum, numerous experiments have been made, in which the corpus luteum secretion has been completely withdrawn by means of castration.

All investigators report hypertrophy of the pituitary gland in castrated animals of both sexes. They also describe changes in the numerical proportion between the three types of cells, etc.

Of the various observations reported, we may accept as proved that the hypophysis is found increased in weight in castrated animals. This enlargement must be considered a compensatory hypertrophy. Even in this connection, however, possibilities of error arise, for the hypophysis under normal conditions gains in weight progressively with the increased age of the animal (Trautmann).

When we turn to the morphological changes, the possibilities for error, and for subjective interpretation of the findings, are greatly increased. Even in the thinnest sections, a bewildering maze of cells is encountered, and sections cut in different planes will give differing pictures. Therefore, before we can accept reports of variations in the numerical proportion of cells, these variations must be so marked as to preclude misinterpretation.

I will spare the reader the task of wading through even the sifted and epitomized mass of literature which has been written on this subject. Not one of the interpretations based on variations in morphology—except that in pregnancy—appears convincing to me.<sup>18, 20</sup>

18. Paulesco, N. C.: *L'hypophyse du cerveau*, I Physiologie, Paris, 1908.

19. Lane-Claypon and Starling: *Proc. Royal Soc.*, 1906, lxxviii, B, 505; Starling: *Lancet*, London, 1905, iv, 579.

20. Delille: *L'hypophyse et la médication hypophysaire*, Paris, 1909.



## MATERIAL AND METHOD

The corpus luteum injections, previously detailed, afforded me the opportunity of studying their effect on the hypophysis as well as on the uterus. At Dr. MacCallum's suggestion I have done so.

The protocols above recorded sufficiently explain the nature of the experiments. Corpus luteum extract was given to castrated animals for periods varying in length up to fifteen days. The hypophysis of normal pregnant and non-pregnant guinea-pigs and rabbits, and of castrated animals not injected with extract, were used for controls. As the hypophyses were too small to permit of subdivision, fixation of each specimen in but one fluid was possible. Alcohol and formaldehyd solution were used. This choice proved unfortunate, as several of the special stains recommended failed to give good results. A good nuclear hematoxylin (DeLafield) with eosin as counterstain gave satisfactory pictures in which the three cardinal varieties of cells could be clearly distinguished.

The hypophyses of twenty-seven rabbits and guinea-pigs were examined. Histological examination showed no recognizable difference between the hypophyses of the castrated animals, injected with corpus luteum extract, and those of the controls.

## OTHER OBSERVATIONS

A few thyroid glands were also examined. The structure of the thyroid is too well known to require special description. Here also no characteristic changes were noted either in the epithelium or in the amount or distribution of the colloid secretion.

The suprarenal glands likewise appeared normal in every respect. Examination of the kidneys showed no degenerative or other changes. This applied both to those animals which had received subcutaneous doses of extract, as well as to those to whom it was given by mouth. Therefore, we may conclude that the extract does not irritate the kidneys.

Although numerous animals died during the course of the experiments, their death cannot, in most instances, be directly ascribed to any specific toxic action of the corpus luteum extract. The administration, furthermore, of such enormous doses as were given (for instance 2 gm. of extract given twice daily to a guinea-pig of 500 gm. weight would correspond to nearly 0.5 kilo of extract daily to a woman weighing 60 kilos) are far in excess of any amount which might be employed in actual therapy.

## SUMMARY OF EXPERIMENTAL RESULTS

The results of this investigation can be summed up most briefly:

1. Corpus luteum extract, injected intravenously in sufficient concentration, proves rapidly fatal in consequence of intravascular thrombosis.
2. Corpus luteum extract of a heterologous species, given subcutaneously, by mouth, or by a combination of these routes, does not replace the normal action of this gland of internal secretion. The injections do not

suffice to "sensitize" the uterus and enable it to produce Loeb's deciduomata and do not bring about such epithelial changes as are noted after follicular rupture.

3. Corpus luteum extract injections call forth no recognizable reaction in the hypophysis.

#### OVOTHERAPY VIEWED IN CONNECTION WITH EXPERIMENTAL RESULTS

Negative results in any investigation always prove disappointing. Nevertheless, in this instance, they possess a practical value. Ovotherapy has for some years been widely employed in an empirical way, either in the form of ovarian extract or of the more specific (?) lutein substance. The results obtained have shown great variations, seemingly depending about equally on the subjective impressions of the physician and of the patient.

That castration exercises an influence on the organism is beyond dispute. The nature of these alterations, however, is by no means constant. In young animals the sexual characteristics, particularly the secondary characteristics, may assume a neutral type, and the normal development of the organs of sex and of the skeleton is usually interfered with. In the adult human being organic alterations, except in the genital apparatus, are minimal, and many of the symptoms complained of are largely psychical, perhaps due to a great extent to a popularly ingrained superstition, amounting to a "phobia."

For many years a profound influence on the general metabolism has been supposed to follow castration. Loewy and Richter,<sup>21</sup> investigating the cause of obesity in castrates, reported diminution of oxidation in both male and female dogs; and a return to above the normal, in both sexes, in response to administration of ovarian (or testicular) substance in the food. Their examinations were limited to the oxygen consumption, and carbon dioxid excretion. The newest, and I may say most thorough work, is that of McCrudden,<sup>22</sup> who did not find the commonly accepted alterations in metabolism, which supposedly follow castration.

Therefore, not only must we be prepared to revise our views on the after-effect of castration, but also, for the present, to assume a judicial attitude toward the contradictory statements, relating to the effects of ovotherapy.

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21. Loewy and Richter: *Berl. klin. Wchnschr.*, 1899, xxxvi, 1095.

22. McCrudden: *Jour. Biol. Chem.*, 1910, vii, 185.

In castrated women, return of the menstrual function, as observed after implantation of ovarian tissue, will afford an unmistakable index of the efficacy of organotherapy; in animals, Loeb's test can be applied.

The symptom most frequently relieved by oötherapy is the so-called flush (sweats, dizziness, etc.) of the natural and artificial menopause. These vasomotor disturbances, most often noted in neurotic women, may persist for a shorter or longer period; may disappear in response to appropriate or inappropriate treatment, and are, therefore, entirely unsuitable as a reliable index for judging the efficacy or potency of any drug.<sup>23</sup>

In the further study of the corpus luteum our efforts should be directed toward exact experimental proof rather than toward empirical generalization. Possibly, by different methods, an active substance may yet be obtained; probably, however, Loeb is correct in saying that "it is very likely that the body fluids are different in the different individuals of the same species." There hinges the difficulty, and the obstacles may prove insurmountable, when we are forced to employ substances derived from a different species, although this generalization finds at least one exception, the case of the thyroid gland.

Further experiments along these lines will be undertaken in the near future. The subject is of too great importance to be dismissed before every effort has been exhausted.

I desire to thank Professor MacCallum for the numerous suggestions, already acknowledged in the body of this article, and for extending the privileges of his laboratory. I am under deep obligations to Dr. Leo Loeb of Philadelphia for his kindness in acquainting me with the technic he has developed and for numerous other courtesies. Dr. Howard Lindemann assisted me throughout the experimental work, and my obligations also include several of the workers in the laboratory, who have materially aided me in many ways.

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23. It would prove of interest, in this connection, to make a careful study of the variations in blood-pressure before and after castration, and the effect (?) of oötherapy under these conditions.

## ANTERIOR POLIOMYELITIS

METHODS OF DIAGNOSIS FROM SPINAL FLUID AND BLOOD IN MONKEYS  
AND IN HUMAN BEINGS\*

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The possibility of successfully combating acute anterior poliomyelitis in human beings depends not only on the prosecution of the recent fruitful experimental studies along the lines of etiology and specific therapy, but also on the establishment of an accurate method of diagnosis. There is perhaps no acute disease which, in its early stages, offers greater difficulties in differential diagnosis. The diagnosis is often impossible even at autopsy. From this very diagnostic difficulty has arisen a certain logical scepticism as to the etiological entity of anterior poliomyelitis, as separable from the forms of meningitis of known causation. The experimental disease, as produced in monkeys by intracerebral injection of an emulsion of the brain or cord of human cases, remains the best and rather persuasive evidence of the specificity of the disease.

This article deals with attempts to find a method of diagnosis from the blood or cerebrospinal fluid in cases of anterior poliomyelitis, both in monkeys<sup>1</sup> and in human beings. Our investigations have proceeded along two lines: first, the examination of the blood or spinal fluid by recognized clinical methods of estimation, and, secondly, by the testing of the fluids by certain biological reactions of immunity.

### *CLINICAL EXAMINATION OF THE BLOOD AND SPINAL FLUID*

CELL STUDY OF THE BLOOD AND SPINAL FLUID IN MONKEYS SUFFERING  
FROM EXPERIMENTAL POLIOMYELITIS

In Table 1 is outlined the clinical course of the experimentally produced disease in six monkeys, which were successfully inoculated with

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\* From the Laboratory of Serum Diagnosis, Harvard Medical School.

<sup>1</sup> Financial aid for this investigation was received from funds given in memory of Mark Wyman Richardson, Jr., and John Archer Richardson, who died of anterior poliomyelitis July 25 and Aug. 5, 1909.

<sup>2</sup> Working under a special grant from the Proctor Fund.

1. The original material for the experimental work in monkeys was obtained through the kindness of Drs. Flexner and Lewis, who furnished us with several strains of the virus.

poliomyelitis virus. In these animals, more or less complete series of observations were made of the blood and spinal fluids before inoculation, during incubation and prodromal symptoms and at intervals in the acute disease.

TABLE 1.—INTRACRANIAL INJECTIONS PRODUCING ACUTE POLIOMYELITIS IN MONKEYS

Monkey No.	Material Used.	Incuba- tion, During Days.	Prodromal Symptoms, Days.	Acute Onset, Day.	Death, Day.	Type of Disease.
1.	Virus K. (Flexner-Lewis), 4 c.c.	7	5 (2 well)	12th	17th*	Marked prodromata; spinal poliomyelitic form.
5.	Emulsion of cord of monkey No. 1, 2 c.c.	2	1	4th	6th	Bulbar, pontine type; respira- tory paralysis.
7.	Emulsion of Cord of No. 273 (Flexner-Lewis), 2 c.c.	5	1	7th	12th	Spinal poliomyelitic form.
9.	Virus M. A. (Flexner- Lewis), 6 c.c.	12	2	15th	40th	Spinal poliomyelitic form.
12.	Emulsion of No. 273, (F.L.), 2 c.c.	4	1	6th	8th	Spinal poliomyelitic form.
15.	Emulsion of Cord of monkey No. 5, 2 c.c.	7	2	10th	10th	Meningitic form.

\* Chloroformed.

TABLE 2.—LEUKOCYTE COUNT IN ACUTE POLIOMYELITIS (MONKEYS)

Monkey.	Before Inocula- tion.	During Incubation.	Prodromal.	Acute Stage— Day After Inoculation.		
1.	20,000	Average, 23,000	11th day, 21,000	12th	19,000	1st
				14th	12,000	3rd
				15th	11,800	4th
				16th	16,600	5th
5.	21,000	2nd day, 21,400	3rd day, 22,400	4th	14,600	1st
				5th	19,600	2nd
7.	40,000	2nd day, 16,600	6th day, 19,800	7th	13,000	1st
				8th	8,000	2nd
				12th	13,000	6th
9.	21,000	Average, 19,900	14th day, 13,600	15th	14,000	1st
				16th	9,000	2nd
				20th	12,900	5th
				24th	19,400	9th
12.	23,000	2nd day, 23,200	4th day, 23,000	6th	18,600	1st
			5th day, 18,000	7th	12,200	2nd
15.	20,000	2nd day, 48,000	9th day, 19,000	10th	9,400	1st
		7th day, 39,000		12th	11,800	2nd

Blood

In Table 2 is given the white blood-cell counts in these successfully inoculated monkeys. In addition to the normal counts (before inoculation) in this series of monkeys, fourteen white counts in nine other

normal monkeys, not included in the above series, gave a mean of 27,114 cells (low 14,200: high 45,000).

From this table it would seem that the leukocyte count remains stationary or suffers slight fluctuations for undetermined reasons, possibly dependent on the type of disease, during the incubation and prodromal stage. There is a consistent fall in the number of leukocytes (leukopenia) early in the acute stages of the disease. That this leukopenia is a real characteristic of the acute stage of experimental poliomyelitis in monkeys is further evidenced by monkeys which were unsuccessfully inoculated with the same virus at the same time, in which cases no such leukocyte fall occurred.

In addition to the leukopenia in the acute stage, differential counts would seem to show significant variations from the normal.

	Normal differential count (mean of 10 cases).	Count in acute stage (mean of 50 estimations).
	%	%
Polymorphonuclears . . . . .	60	40
Large mononuclears . . . . .	25 } 37	15 }
Lymphocytes . . . . .	12 }	40 } 55
Eosinophils . . . . .	3	5

There is present, then, in the acute stage of the disease, a slight lymphocytosis and a slight eosinophilia. A distinct eosinophilia has likewise been noted in human cases by Lebrede and Recio.<sup>2</sup>

*Spinal Fluid*

In Table 3 is summarized the cell findings in the spinal fluids in the six "positive" monkeys.

The spinal fluid shows marked and very characteristic changes during the incubation period, prodromal stage, and acute stage, which disappear about the time that the acute symptoms begin to subside. These changes are most notable either in the prodromal stage or in the first or second day of the acute stage. Before inoculation it is often impossible to get even one drop of spinal fluid from a lumbar puncture; most of our attempts gave nothing more than dry taps. When successful, there were only one or two cells to be seen in an ordinary Thoma-Zeiss counting chamber,<sup>3</sup> which on staining were apparently large mononuclear or plasma cells. During the incubation period, there is a marked increase

2. Lebrede and Recio: *Poliomyelitis Anterior Aguda Epidemica, Sanidad y Beneficencia (Havana)*, 1910, iii, 170.

3. These cell counts of the spinal fluid are made in a uniform manner by using a drop of the freshly drawn fluid in a Thoma-Zeiss apparatus, as in the ordinary leukocyte count.

in the amount of fluid obtainable from lumbar puncture and the cells in the fluid are very markedly and characteristically increased in number, anywhere from 100 to 300 cells per cubic millimeter being found. These cells are mainly of the large mononuclear type with some polynuclear cells and lymphocytes. In the prodromal stage, there is even a more marked increase in the number of cells, which often reach 1,000 per cubic millimeter. In this stage, also, polynuclears are still present, in some cases as high as 60 per cent., though the large mononuclears and lympho-

TABLE 3.—SPINAL FLUID IN ACUTE POLIOMYELITIS (MONKEYS)

Monkey.	Before Inoculation.	During Incubation.	Prodromal.	Acute Stage.
1.	Two cells seen—1 large mononuclear, 1 small (?) plasma cell.	Sixth day: 100 cells per cu. mm.; large mononuclears 40 per cent.; small (lymphocytes) 60 per cent.	Tenth day: 240 cells per cu. mm.; large and small mononuclears 60 per cent.; lymphocytes 40 per cent.	Fourteenth day: 400 cells per cu. mm.; mostly lymphocytes; 16th day: 60 cells per cu. mm.; lymphocytes; a few polynuclears.
5.	Dry tap.	.....	Third day: 1,000 cells per cu. mm.; polynuclears 60 per cent.; mononuclears 40 per cent.	Fourth day: 800 cells per cu. mm.; 5th day: 1,000 cells per cu. mm.; lymphocytes and polynuclears; young cells undifferentiated.
7.	No cells seen.	.....	Sixth day: 160 cells per cu. mm.; excess of large mononuclears.	Seventh day: 120 cells per cu. mm.; lymphocytes; 8th day: 90 cells per cu. mm.; lymphocytes; 12th day: 20 cells per cu. mm.; large mononuclears; a few polynuclears.
9.	One (?) plasma cell.	.....	Fourteenth day: 120 cells to cu. mm.; lymphocytes 40 per cent.; large mononuclears 60 per cent.	Sixteenth day: 200 cells per cu. mm.; all lymphocytes or small mononuclears (young cells).
12.	Dry tap.	.....	.....	Seventh day: 80 cells to cu. mm.; lymphocytes $\pm$ .
15.	A few large cells and 1 (?) plasma cell.	Sixth day: 300 cells to cu. mm.; large mononuclears 60 per cent.	Ninth day: 150 cells to cu. mm.; large mononuclears 30 per cent.; lymphocytes 60 per cent.; polynuclears 10 per cent.	Tenth day: 180 cells per cu. mm.; lymphocytes $\pm$ ; 30th day: few polynuclears found.

cytes are very evident. In the early acute stage the increase in number of cells is also very marked, the cells, however, now being mostly lymphocytes or undifferentiated cells. As the cells decrease in number, the polynuclears begin to reappear and, at the end of a week or ten days, there are very few cells present, mostly large mononuclears with a few polynuclears.

In the prodromal and acute stages, there is at times a fibrin clot. This clot disappears fairly early during the acute stage. The fluid in our

monkeys was never under any great pressure, though the amount was sometimes increased so that 5 c.c. was easily withdrawn. This occurred with fair regularity in the meningeal type of the infection.

BLOOD AND SPINAL FLUID IN HUMAN CASES OF ANTERIOR POLIOMYELITIS

A comparison of these experimental findings with the findings in four cases of acute poliomyelitis in children is of considerable value (Table 4). The four patients were seen first between the second and fifth day of the acute onset. All of them had a slight fever and were still in the hyper-sensitive state with commencing paralysis, so that the first findings in

TABLE 4.—HUMAN CASES  
CASE 1.—R. H., 20 Months Old

Day.	Temperature.	Blood.	Spinal Fluid.
5th	100	W. B. C.—17,400 dif. lymphocytosis.	10 c.c.: 180 cells per cu. mm.; no clot; lymphocytosis 98 per cent.
8th	100	W. B. C.—12,000 lymphocytosis.	20 c.c.: 50 cells per cu. mm.; no clot; mononuclears, degenerated forms.
13th	99	W. B. C.—11,600.	10 c.c.: 80 cells per cu. mm.; no clot; large mononuclears and degenerated forms.

CASE 2.—E. R., 9 Months

2nd	100	W. B. C.—10,000 lymphocytosis 62 per cent.	5 c.c. clear; clot in 24 hours; 350 cells per cu. mm.; degenerated mononuclears.
5th	98.5	.....	Bloody fluid with clot +; 20 c.c.; very few leukocytes.
7th	100	W. B. C.—7,800 sl. lymphocytosis.	35 c.c.; bloody fluid; clot ++; few degenerated mononuclears.
9th	99.5	W. B. C.—12,200.	.....
12th	100	.....	30 c.c. clear; clot ++; 80 cells per cu. mm.; mononuclears only seen.
17th	100	W. B. C.—11,800.	30 c.c.; first lot clear, sl. clot; 80 cells to cu. mm.; mononuclears +; third lot opaque; clot +; 580 cells per cu. mm.; mononuclears and lymphocytes.

CASE 3.—S. L., 2 Years

4th	101	12,000 normal dif.	50 c.c. clear; no clot; high pressure; 60 cells per cu. mm.
....	100	.....	25 c.c. clear; 510 cells per cu. mm.; mononuclears and lymphocytes.
10th	...	.....	10 c.c. clear; 240 cells per cu. mm.

CASE 4.—N. S., 5 Years

4th	99	13,400 dif. polynuclears 75.5; mononuclears 24.5.	20 c.c. clear; fibrin clot +; 50 cells per cu. mm.; degenerated small and large mononuclears.
5th	...	.....	30 c.c. clear fluid; 130 cells per cu. mm.; mononuclears and lymphocytes.



these cases are comparable with our findings in the early acute stage of our experimental studies. It will be seen from the table that the blood-findings show a moderate, to a marked drop in the white blood-count,<sup>4</sup> with a lymphocytosis,<sup>5</sup> moderately marked in all but one of the cases, which was the one examined latest. The spinal fluid findings are very interesting in all these cases, from the fact that, in two of them, definite fibrin formation was present early, which disappeared rapidly in one and very slowly in the other. The increase in the number of cells was still present in two cases, as late as the twentieth day after the acute onset. The type of cells found was practically the same as in the monkey spinal fluids, the lymphocytes and small mononuclears predominating on the first examinations, later being replaced by large mononuclears, and in the last findings polynuclears beginning to reappear.

#### *BIOLOGICAL TESTS WITH BLOOD-SERUM AND SPINAL FLUID*

The best-known and most successful of the biological methods of diagnosis from the blood is the fixation reaction of Bordet and Gengou. This reaction serves to detect the presence of either an antigen or an antibody in a mixture, when the other of the two substances is known to be present. Its applicability is found to be very wide; it occurs in infections due to bacteria, as, for example, in typhoid fever, in which disease antibodies may be demonstrated more constantly earlier in the disease than agglutinins (Widal reaction). The fixation reaction has also been found in protozoan infections and in diseases of unknown etiology like cancer.

The fixation reaction has already been tried in anterior poliomyelitis by at least two authors. Wollstein<sup>6</sup> took the lumbar puncture fluid from patients with the disease and, with this fluid as an antigen, tested for the presence of antibodies in the blood-serum and cerebrospinal fluid of recovered patients. Extracts of medulla, spinal cord and other organs were likewise employed as antigens,<sup>7</sup> and the blood from patients in various stages of the disease, as well as from recovered patients, tested in combination with them. In spite of varied, extensive, and well-controlled experiments, Wollstein's results were uniformly negative. In a more recent study of an epidemic of poliomyelitis in Cuba, Lebrede and Recio<sup>2</sup> claim to have obtained a fixation reaction in one of three cases tested, employing the serum of recovered patients as an antiserum and, as

4. Normal white count in children under 2 years is from 12,000 to 15,000; from 2 to 5 years, 10,000.

5. Lymphocytosis is a common finding in infancy.

6. Wollstein: Biological Study of the Cerebro-spinal Fluid in Anterior Poliomyelitis, *Jour. Exp. Med.*, 1908, x, 476.

antigens, extracts of various organs from a patient in a prolonged febrile case who died on the eleventh day. In consideration of the complexity of this reaction and its multiple sources of error, reports which fail to outline the method employed, and which report a single positive result, can scarcely be accepted as more than suggestive evidence.

We have tried the fixation reaction with materials obtained both from monkeys and from human beings. Our experiments vary in conditions from those of the authors cited, and may be divided into two general series.

#### FIXATION EXPERIMENTS, SERIES I

*Antiscrum.*—Monkey 6 (*Macacus rhcsus*) was given 3 c.c. of virus "M. A." (Flexner-Lewis) into the cerebrum on March 9, 1910, which virus produced the disease in Monkey 9 (see Table 1). Monkey 6 showed no symptoms, and on April 6 was given subcutaneously an emulsion of brain from Monkey 1, which produced the disease in two of five other monkeys to which it was given. The emulsion employed for immunizing Monkey 6 had been preserved with 0.5 per cent. phenol solution, and so differed from the virus emulsion employed on the other five. Injections were repeated subcutaneously (4 c.c.) on April 16, 21, 26, and May 3 and 9. The animal was anesthetized and bled partially nine days later. The serum of this monkey, antiserum 6, was heated to 56 C. for one-half hour and tested for fixation with the following possibly antigenic fluids.

*Antigens.*—Blood or cerebrospinal fluids (later specified) from cases of poliomyelitis in monkeys and in human beings.

*Technic.*—Mixtures were made of 0.4 c.c. of the antiserum from Monkey 6, heated to 56 C. plus 0.2 c.c. of the fluids tested for antigen (blood-serum previously heated to 56 C.), plus fresh guinea-pig serum (alexin), 0.1 c.c. in 1 c.c. of a 0.9 per cent. salt solution. Contact was allowed at 37 C. for one hour and then 1 c.c. of a 5 per cent. suspension of washed sheep blood plus 1 c.c. of saline solution containing three hemolytic doses of rabbit antsheep serum (56 C.) was added. Hemolysis was observed at 37 C. for two hours. Controls were likewise made of each antigenic serum alone and of the antiserum alone plus alexin.

By this method the following fluids were tested for antigens:

1. Spinal fluid, normal Monkey 5.....
2. Spinal fluid, Monkey 1..... Anterior poliomyelitis, 2d day.
3. Spinal fluid, Monkey 4..... Unsuccessfully inoculated with virus.
4. Spinal fluid, Monkey 6..... Unsuccessfully inoculated with virus.
5. Spinal fluid, human case A..... Influenza meningitis.
6. Spinal fluid, human case E. R..... Eighth day of acute poliomyelitis.
7. Spinal fluid, human case L. B..... Influenza meningitis.
8. Spinal fluid, human case D..... Hydrocephalus.
9. Spinal fluid, human case S..... Poliomyelitis, 6th day.
10. Spinal fluid, human case R. R..... Poliomyelitis, 8th day.
11. Spinal fluid, human case Z..... Poliomyelitis, 3d day.
12. Spinal fluid, human case X..... Tuberculous meningitis.
13. Serum, Monkey 1..... Anterior poliomyelitis, 3d day.
14. Serum, Monkey 9..... Anterior poliomyelitis.
15. Serum, normal Monkey 8.....
16. Virus, emulsion of cord of Monkey 1.
17. Virus, emulsion of brain of Monkey 1.

With none of these fluids was there any evidence of fixation with the serum of Monkey 6, not even with the antigenic emulsion of the cord and brain of Monkey 1, which had been used to immunize Monkey 6. It would perhaps be desirable to employ the serum of a monkey that had spontaneously recovered from the disease and then been reinoculated with active virus as an antiserum in such experiments.

#### FIXATION EXPERIMENTS, SERIES II

In this series antibodies were sought for in the blood-serum of monkeys in various stages of acute poliomyelitis, in unsuccessfully inoculated monkeys, and, as controls, in normal monkeys. As an antigen, an emulsion of spinal cord of Monkey 1 which had been mechanically shaken with four volumes of phenolated salt solution was employed. In control tubes, an emulsion of the spinal cord of a normal monkey replaced the antigenic cord. The following monkey serums were tested for antibodies in this manner:

1. Serum of Monkey 1, 56 C.....Two days after inoculation.
2. Serum of Monkey 1, 56 C.....Three days before symptoms.
3. Serum of Monkey 1, 56 C.....Second day of acute symptoms of poliomyelitis.
4. Serum of Monkey 1, 56 C.....Fourth day of acute symptoms of poliomyelitis.
5. Serum of Monkey 1, 56 C.....Fifth day of acute symptoms of poliomyelitis.
6. Serum of Monkey 2, 56 C.....Two days after negative inoculation.
7. Serum of Monkey 4, 56 C.....Two days after negative inoculation.
8. Serum of Monkey 5, 56 C.....Six days after negative inoculation.
9. Serum of Monkey 5, 56 C.....Eleven days after negative inoculation.
10. Serum of Monkey 6, 56 C.....Normal.
11. Serum of Monkey 6, 56 C.....Five days after negative inoculation.
12. Serum of Monkey 6, 56 C.....Eight days after negative inoculation.
13. Serum of Monkey 6, 56 C.....Eleven days after negative inoculation.
14. Serum of normal Monkey 7.....
15. Serum of normal Monkey 9.....
16. Serum of normal Monkey 10.....

In none of these serums was there evidence of alexin fixation.

#### CONCLUSIONS

The acute stage of anterior poliomyelitis, as it occurs in human beings, and as it is produced experimentally in monkeys, is characterized by the occurrence of a distinct leukopenia. The differential count shows a relative increase in number of eosinophils and lymphocytes. As studied experimentally in monkeys, the leukopenia of the acute stage is not preceded by any constant leukocyte picture.

The spinal fluid in poliomyelitis monkeys shows more marked and characteristic findings. There is a marked increase in the number of cells during incubation and prodromal stages and the early days of the acute period, being highest in the prodromal stage. The increased cells are at first mononuclear in type and are later replaced by polymorphonuclear cells. A fibrin clot appears in the prodromal and early acute stages.

but disappears later. These findings in monkeys agree with the findings in human beings, so far as our observations extend.

Tests for antibodies to the poliomyelitis virus and for antigens to a supposed antiserum to poliomyelitis (blood of animal repeatedly inoculated with active and then inactivated virus) were made by means of the Bordet-Gengou fixation reaction. There was no evidence of antibodies in the serum of monkeys taken at intervals during the acute disease or in the serum of unsuccessfully inoculated monkeys. There was no evidence of the antigen in the spinal fluids of monkeys or of human beings at various stages in the disease, or in the blood-serum of monkeys suffering from the disease. These latter results corroborate and extend the negative findings of Wollstein.

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## THE HEART MUSCLE IN TYPHOID FEVER

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### INTRODUCTION

Some years ago, following a suggestion made by Dr. W. S. Thayer, I undertook to study the condition of the heart muscle of patients who had died of typhoid fever in the Johns Hopkins Hospital. It has long been a custom in the pathological department to save portions of the organs from all autopsies. Such portions have been hardened in Müller's or Zenker's fluid and preserved in alcohol. With the consent of Dr. Welch this material was placed at my disposal. From the autopsy records I selected for study fifty consecutive cases of death during typhoid fever. In seven instances no heart muscle had been preserved, so that the number to be studied was reduced to forty-three. The portion of the heart muscle found consisted of one or more strips from the left ventricle. From various portions of these strips, small blocks were cut and imbedded in celloidin or paraffin. The sections were for the most part stained in hematoxylin and eosin, although carmin and Van Gieson's stain were also used. The number of blocks to a given case varied from two to ten. In all, sections from 19½ blocks were studied. The clinical features of each case were ascertained from the medical records, which are unusually full. The general autopsy findings were readily available in the fasciculi of the pathological department.

I have realized from the beginning how incomplete the conclusions based on such fragmentary evidence must be. From small bits of the left ventricle one is not justified in drawing conclusions about the heart as a whole. If a lesion is present it may be isolated; if it is absent it may exist in other parts of the heart. Only some method such as Krehl's,<sup>1</sup> in which the whole organ is cut into small blocks and sections from each studied, can be considered thorough. It is noteworthy, however, that in cases in which a lesion of any extent, and particularly an interstitial lesion, was found, it was present in all of the slides from that particular case and in cases in which no marked changes existed, none of the slides have shown them. It is quite true that some portions of the heart muscle show lesions more extensively than others and the variation in

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1. Krehl: *Deutsch. Arch. f. klin. Med.*, 1890, xlv, 484.

this respect may introduce a serious error of judgment. The work, however, is presented with this deficiency clearly in mind. I merely hope that in a general way it may emphasize an important lesion of typhoid fever and show its relation to equally important and interesting clinical symptoms.

#### HISTORICAL REVIEW

The condition of the heart in typhoid fever was first commented on in the early part of the last century and studied with care twenty and thirty years ago. At that time it attracted considerable interest and received its fair share of literary attention. Its importance was fully realized and little has been added to what was then written about it. With the rather general abandonment of morphological investigation, due to the exhaustion of the possibilities of existing methods, this field has lost its attraction. In the literature of the past ten years scarcely an article of importance has appeared and one will search the *Index Medicus* for the past five years in vain. Laennec<sup>2</sup> and after him Louis<sup>3</sup> speak of the softness of the heart muscle in typhoid fever and of the yellowish mottled coloring—the dead-leaf appearance. Louis compared it to a wet cloth which will retain any form into which it may be pressed. He makes these lesions the explanation of certain changes observed in the pulse, an association already guessed at by Laennec. Stokes,<sup>4</sup> in his book on the heart, published in 1854, gives a much fuller description of the changes than Louis did and points their relation to clinical symptoms with more precision. Virchow,<sup>5</sup> in 1852, gave an accurate description of the microscopical fiber changes which he considered inflammatory and his views were elaborated by Böttcher.<sup>6</sup> The first extensive and complete consideration of the subject is by Hayem,<sup>7</sup> in 1869. In a study of four cases of typhoid fever with sudden death he describes in detail the fiber lesions and for the first time draws attention to the interstitial changes which in subsequent contributions assume so much importance. He lays great emphasis, too, on changes in the coronary arteries, notably a wide-spread endarteritis of the small vessels, which he considers the direct cause of

2. Laennec: *Traité de l'auscultation médiate*, Paris, 1819, p. 815.

3. Louis: *Researches on Typhoid Fever*, Transl. by Bowditch, Boston, 1836, p. 282.

4. Stokes: *Diseases of the Heart and the Aorta*, Dublin, 1854.

5. Virchow: *Virchow's Arch. f. path. Anat.*, 1852, iv, 261.

6. Böttcher: *Ueber Ernährung und Zerfall der Muskelfasern*, *Virchow's Arch. f. path. Anat.*, 1858, xiii, 236.

7. Hayem: *Recherches sur les rapports existant entre la mort subite et les altérations vasculaires du cœur dans la fièvre typhoïde*, *Arch. de physiol.*, 1869, ii, 699.

death. His observations were preceded by the notable contribution of Zenker<sup>8</sup> on the lesions of the voluntary muscles in typhoid fever. Zenker had noted in one of his cases extensive granular degeneration of the heart muscle. Following Hayem's paper there appeared a large number of publications on sudden death in typhoid fever and the concomitant heart changes. A clinical type was set up, described as the "forme cardiaque de la fièvre typhoïde." The most notable contributions are from Hayem,<sup>9</sup> Huchard,<sup>10</sup> Landouzy and Siredey,<sup>11</sup> Déjerine<sup>12</sup> and Willaume.<sup>13</sup> In Germany the studies of Birch-Hirschfeld<sup>14</sup> and Leyden<sup>15</sup> on diphtheria myocarditis extended the knowledge of interstitial lesions. In 1891 Ernst Romberg<sup>16</sup> published a most complete review of heart changes in typhoid fever, scarlet fever and diphtheria. In a careful study of 11 hearts from patients dying of typhoid fever he noted granular degeneration marked in 3 and moderate in 1; fatty degeneration marked in 2, moderate in 4 and absent in 5; hyalin degeneration slight in 2 and absent in 9. Segmentation was common. Many fibers showed vacuolar degeneration and, on cross-section, increase in the sarcoplasm. Nuclear changes were marked but not as extensive as in diphtheria. Interstitial infiltration he found marked in 2 instances, moderate in 3, slight in 1 and absent in 5. In a very suggestive way he brings these lesions into relation with the circulatory symptoms observed during life. Picot<sup>17</sup> has substantiated Romberg's findings and nothing of importance has been added to the subject since then.

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8. Zenker: Ueber die Veränderungen der willkürlichen Muskeln im Typhus abdominalis, Leipsic, 1864.

9. Hayem: Des manifestations cardiaques de la fièvre typhoïde, Progrès méd., 1875. Quoted by Renaut: Cong. franç. de méd., 1899, ii, 1.

10. Huchard: Etude critique sur la pathogénie de la mort subite dans la fièvre typhoïde, Union méd., 1877. Quoted by Renaut: Cong. franç. de méd., 1899.

11. Landouzy and Siredey: Etudes sur les localisations angio-cardiaques typhoïdiques: leurs conséquences immédiates, prochaines et éloignées, Rev. de méd., 1887, vii, 804.

12. Déjerine: Sur les altérations du myocarde comme cause de mort subite dans la fièvre typhoïde, Soc. de biol., December, 1885. Quoted by Renaut.

13. Willaume: De la forme cardiaque de la fièvre typhoïde, Thèse de Nancy, 1887.

14. Birch-Hirschfeld: Quoted by Romberg: Deutsch Arch. f. klin. med., 1891, xlviii, 369.

15. Leyden: Ueber die Herzaffectationen bei der Diphtherie, Ztschr. f. klin. Med., 1882, iv, 334.

16. Romberg: Ueber die Erkrankungen des Herzmuskels bei Typhus abdominalis, Scharlach und Diphtherie, Deutsch. Arch. f. klin. Med., 1891, xlviii, 369.

17. Picot: Semaine méd., 1894, xiv, 57.

## THE ANATOMICAL LESIONS OF THE HEART MUSCLE IN TYPHOID FEVER

It is difficult to make any detailed classification of the gross cardiac lesions described in the pathological records, but certain almost constant findings stand out prominently. The effects of granular and fatty degeneration are particularly striking. In nearly all instances the muscle is described as paler than normal and soft in consistency. In one instance the note is made that the ventricle walls retain the impression of the fingers wherever they are pressed; in another, that the heart collapses over the hand. The color is variously described as brownish-red, light brown, etc., but gray and yellow predominate. In appearance it is nearly always described as opaque or cloudy or as showing the mottling characteristic of fatty degeneration. Small hemorrhages are frequently noted

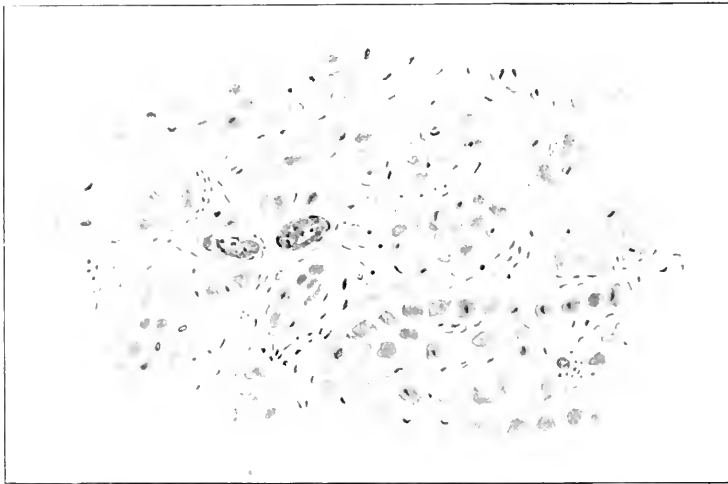


Fig. 1.—Series 9; marked degeneration and atrophy of muscle fibers.

and in a few instances grayish or yellowish areas characteristic of foci of interstitial infiltration or complete fiber degeneration. In only seven instances is the muscle described as firm and little altered in appearance. Fresh sclerosis of the aorta and coronaries was noted eight times and as all but one of these observations were made at recent autopsies it is probable that the lesion has occurred more commonly than described.

For descriptive purposes it is convenient to divide the histological changes into fiber lesions, interstitial lesions and vascular lesions.

The most common changes that one finds in the muscle fibers of the heart in acute infectious diseases, namely, granular and fatty degeneration, are not very evident in the sections studied. The hardening and



preservation of the tissue would, of course, remove any fat that may have been present and obscure the albuminous granules. Such pictures of granular degeneration as one sees in fresh specimens have never been encountered. Still, many of the fibers show a well-marked granular appearance. It is the granular degeneration that makes the striation appear indistinct in many fibers. In only one instance were fibers seen that seemed to have undergone hyaline degeneration, and these *en masse* in a single area. Amyloid degeneration was not observed.



Fig. 2.—Series 9; degenerated muscle fibers with large vacuoles.

Many of the fibers show a distinct loss of striation, although marked alterations were noted in only four instances. The transverse bands are affected more frequently than the longitudinal. At times large vacuoles are noted in the fibers often traversed by indistinct striæ. Occasionally a whole fiber is degenerated and filled with these irregular vacuoles.

In one instance there seems to be a wide-spread atrophy of the muscle cells, a lesion to which Drago<sup>18</sup> particularly has called attention. The

18. Drago: Beiträge zur Histopathologie des Typhusherzens. Beitr. z. path. Anat. zu allg. Path., 1901, xxix, 142.

muscle bundles are widely separated and between the shrunken individual fibers are large interspaces filled with a coagulated serous fluid studded with a few connective tissue cells and a few leucocytes. Vacant spaces show where fibers have completely disappeared (Fig. 1).

On cross-section changes are often still more evident. The fibril bundles are small and widely separated. Their number is frequently decreased and a large area of the heart muscle may be composed of fibers with only a peripheral zone of fibril bundles somewhat resembling, under

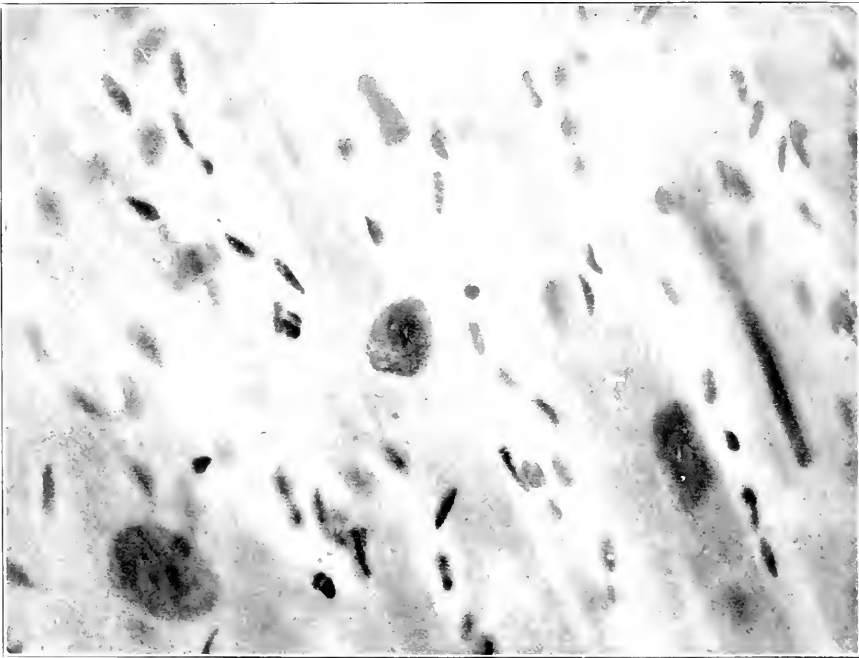


Fig. 3.—Series 9: large vesicular nuclei. From photomicrograph by Dr. M. C. Winternitz.

the low power, adipose tissue. Vacuolization is particularly well seen in some instances (Fig. 2). Krehl suggested that these vacuoles were spaces from which fat had been dissolved. There is, however, nothing to support such a view and it has been discarded.

Fragmentation is one of the commonest of the lesions. It was present in twenty-five instances and extensive in eleven. It varies from an

unusual distinctness of the "cement lines" to complete separation of the fibers, often with dislocation.<sup>19</sup>

The most constant of all the fiber lesions are changes in the nuclei. Not a single specimen but shows them to some degree; and in thirty-two instances they were well marked. The perinuclear spaces are enlarged and there is an accumulation of pigment granules at the poles. Frequently two nuclei lie side by side and occasionally in such a manner as to suggest division. The nuclei themselves show most far-reaching changes. They are swollen, often to four or five times their usual dimension, are vesicular and filled with a few irregular strands of chromatin. Many look like empty pouches and others show the most irregular and bizarre outlines (Fig. 3).

The interstitial changes have particularly attracted my attention. Well-marked interstitial edema was noted in eight cases and extensive hemorrhages in six. In about one-half of the cases there is a noticeable increase in the cells in the interstitial tissue. These consist of scattered small mononuclear cells and some large mononuclears and an occasional polymorphonuclear. The cells are grouped principally about the blood-vessels. Of more importance are the focal accumulations of cells first described by Hayem and later emphasized by Rouberg. These foci may, as Ribbert<sup>20</sup> claims, be divided into two types. The foci of the first type consist almost entirely of small round cells and resemble lymphoid nodules. Ribbert, indeed, believes that they represent hypertrophy of normal lymphoid structures. They are found principally under the epicardium and occasionally under the endocardium. In some cases they form an almost continuous band under the epicardium, with here and there nodular enlargements. More commonly they are small groups of cells which show little tendency to dip down between the muscle bundles, although in the papillary muscles limited invasion is sometimes seen. Exceptionally similar nodules occur in the connective tissue spaces between the muscle bundles.

The second type of cellular accumulation is more intense and extensive. In different specimens the kind of cell and the relative proportion

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19. Newer anatomical studies have demonstrated that the cardiac musculature is a syncytial tissue and is not divided into distinct cells. The cement lines which were formerly regarded as marking the outlines of the cell and being the point of contact of adjoining cells are areas of irregular contraction. They have the same significance as fragmentation. See Aschoff and Tawara: *Die heutige Lehre von dem pathologisch-anatomischen Grundlagen der Herzschwäche*, Jena, 1906.

20. Ribbert: *Ueber Myocarderkrankungen nach Diphtherie*, Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1900, v. 1.

of the different cells vary. Most commonly the small round cell predominates with a liberal interspersing of large mononuclear cells and some polymorphonuclears. All the areas contain, too, certain large endothe-



Fig. 4.—Series 27: an area of infiltration consisting almost entirely of large cells with oval eccentric nuclei.

lioid cells with round or oval eccentrically placed nuclei. A few of these cells had acted as phagocytes. In one instance they were the predominating, indeed, almost the only type of cell present (Fig. 4). In another

instance there is an astonishingly large number of eosinophils (Fig. 5). These cell accumulations arise frequently beneath the epicardium or endocardium and dip deeply down into the muscle running irregularly between the bundles and along the course of the blood-vessels (Figs. 6 to 10). Others occur as foci within the muscle itself when their relation to the blood-vessels is particularly striking. In nearly all instances they arise

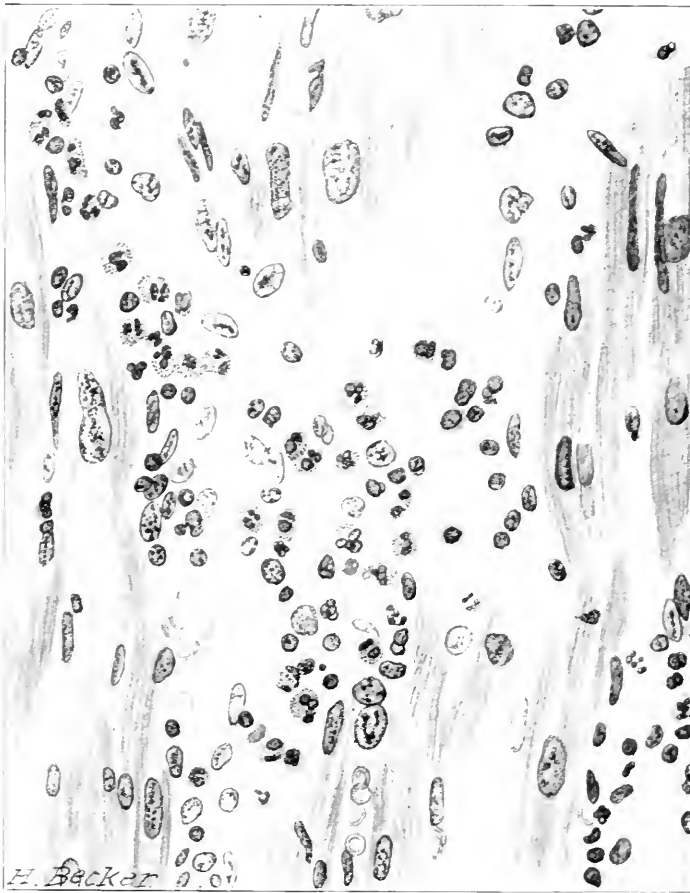


Fig. 5.—Series 31: the large number of eosinophils is noteworthy.

in the connective tissue bands about a medium-sized vessel and from this base pierce irregularly between the muscle bundles and cells. I have looked particularly to ascertain the relation of these bands of cellular infiltration to degeneration of the muscle cells. I may say confidently that they are not limited to areas where the fiber changes are most strik-

ing, and, indeed, seem to bear no definite relation to the fiber lesions. The papillary muscles are a favorite site for these interstitial changes, although as a rule they are not most extensive there. Such interstitial cellular accumulations were observed in twenty-nine cases and in fifteen they were rather intense and extensive. In many sections showing the presence of old chronic fibroid lesions these areas are the seat too of an acute inflammatory reaction. The bundles of degenerated fibers and the fibrous tissue itself are surrounded and infiltrated by leucocytes and red blood corpuscles.



Fig. 6.—Series 5: area of filtration in and under the endocardium with some invasion between muscle fibers. The cells consist of small and large mononuclears with many of the large cells with eccentrically placed nuclei and homogenous eosin-staining protoplasm. From photomicrograph by Dr. M. C. Winternitz.

The blood-vessels in most sections are unusually full. The capillaries stand out prominently and are engorged. Some of the larger vessels in the pericardium show an acute periarteritis (Fig. 11). In five cases there is a definite endarteritis in the coronary arteries and this lesion would undoubtedly have been more frequently found had more sections included portions of the coronaries. Nothing in any way approaching

the extensive endarteritis in the small vessels described by Hayem was observed. Occasionally the endothelial cells appear swollen and there is a slight accumulation of round cells in the media.

#### THE PATHOGENESIS OF THE HEART MUSCLE LESIONS

Renaut,<sup>21</sup> following the experimental work done in his laboratory by Mollard and Regaud,<sup>22</sup> gives a simple explanation of the sequence of



Fig. 7.—Series 31: area of extensive infiltration under the epicardium. These are marked areas of hemorrhage. The small mononuclear cells predominate, but there are many large mononuclears and a few large endothelioid cells. Eosinophils are particularly abundant. (Specimen from same case as Fig. 5.) From photomicrograph by Dr. M. C. Winternitz.

21. Renaut: *Les myocardites aiguës*, Cong. franç. de med., 1899, ii, 1.

22. Mollard and Regaud: *Contribution à l'étude expérimentale des myocardites*, Ann. de l'Inst. Pasteur, 1897, xi, 97.

events in the myocardial lesions of acute infectious diseases. Although the work of Mollard and Regaud was performed with diphtheria toxin, the lesions produced are so similar to those of typhoid fever that the principles established for one might be readily applicable to the other. The changes are divided into four stages:

1. The lesions of attack. These are the immediate results of the action of the toxin. They occur only in the muscle fibers and may be the sole change when death follows quickly. The lesion consists of granu-



Fig. 8.—Series 9: an area of infiltration beginning under the epicardium and infiltrating the muscle. Although there are many small mononuclear cells, they are surrounded by an unusually rich zone of cell protoplasm. Many large mononuclear cells with vesicular nuclei. An occasional pus cell. From photomicrograph by Dr. M. C. Winternitz.

lar degeneration, followed by a more uniform staining with eosin and disappearance of cross-striation. On transverse section the fields of Cohnheim are diminished in size and later disappear, leaving a homogeneous appearance. There may be a general hyperleukocytosis.



2. The defense reaction of the heart cells. Cohnheim's fields become still more obscured and the spaces between the cylinders of Leydig enlarged. The fibers become vacuolar and this change is followed by an extensive fatty degeneration. There is a marked increase in the amount of sarcoplasm which may exude into the interspace between the cells. Nuclear changes are common and segmentation and fragmentation frequently occur.



Fig. 9.—Series 43; area of extensive infiltration in a papillary muscle. Character of cells about same as in previous figures. From photomicrograph by Dr. M. C. Winternitz.

3. Liquidation of the muscle fibers. Up to this time there has been only an increase of the small mononuclear cells in the blood-vessels themselves. There is now a general pouring out of leukocytes about the dying cells, which then rapidly undergo solution.

1. With the disappearance of the leukocytes, fibrous tissue is formed and months afterward a scar is left as the result of the primary damage to the muscle fibers.

The damage to the muscle cell is then the first and the essential cardiac lesion of infectious diseases and the interstitial changes are merely consequent on this. Renaut rejects any idea of a primary interstitial inflammation. He lays great emphasis on the fact that Mollard and Regaud find that areas of interstitial infiltration never occur before the twelfth day. This fits well into his view. He comments, too, that

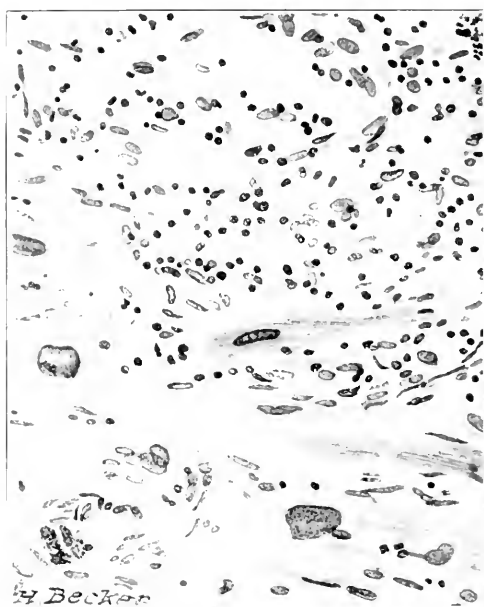


Fig. 10.—Series 34; an area of infiltration under the epicardium showing the usual type of infiltrating cells.

we never see a pure interstitial myocarditis, while changes in the fibers alone occur frequently.

The histological picture of the hearts I have studied does not support this simple explanation of Renaut's. As Romberg has pointed out, and Krehl<sup>23</sup> has emphasized, the areas of interstitial infiltration bear no direct relation to the fiber lesions. They are by no means most marked where the fiber changes are severest and frequently surround healthy muscle cells. Their intimate relation to the blood-vessels, as previously com-

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23. Krehl: *Erkrankungen des Herzmuskels*, Nothnagel's System, 1901, p. 283.

mented on, is a much more striking association. It seems scarcely possible that their extravasation could be directly due to an attraction offered by the dying muscle cells. That they occur later than the fiber lesions is no direct proof of their secondary nature.

#### THE CIRCULATORY SYMPTOMS OF TYPHOID FEVER

In studying the clinical records of my cases only the unusual circulatory symptoms have been selected. The changes in rate and pressure and the general phenomena of failing circulation which appear before

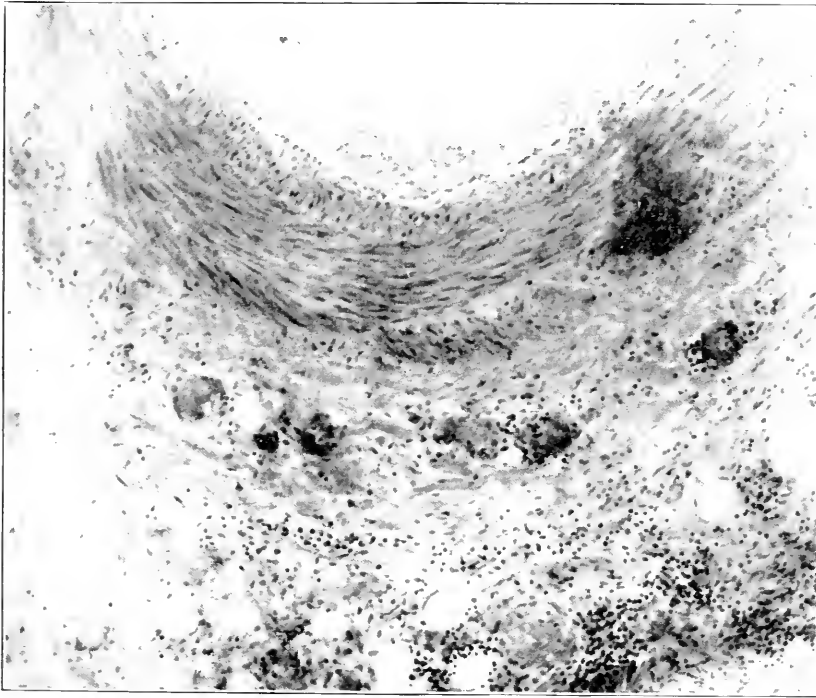


Fig. 11.—Series 9: periarteritis of the coronary artery. From photomicrograph by Dr. M. C. Winternitz.

death and are common to all infections have not been regarded. What I have sought for particularly are those symptoms which for days and even weeks lead one to assume the presence of cardiac damage and to

24. The circulatory symptoms of 1,458 cases of typhoid fever studied in the wards of the Johns Hopkins Hospital have been carefully analyzed by Thayer: *On the Cardiac and Vascular Complications and Sequels of Typhoid Fever*, *Bull. Johns Hopkins Hosp.*, 1904, xv, 322.

anticipate a fatal termination. Such circulatory symptoms are far less prominent in typhoid fever than in diphtheria or scarlet fever. Still, at least in my fatal cases, they are by no means uncommon. It may be said that in the routine observation of our patients no unusual diagnostic *finesse* has been directed to the condition of the heart and circulation.

Of the forty-three cases studied the clinical records of two have been lost. Of the remaining forty-one cases eleven showed prominent circulatory symptoms, twelve less marked but definite circulatory symptoms and eighteen no unusual circulatory symptoms.

Five patients had a pulse-rate unusually rapid and out of all proportion to the temperature and general symptoms. Huchard begins his book on diseases of the heart with the description of a typhoid patient with this symptom and emphasizes its grave significance. The pulse was unusually slow and irregular in one case. In sixteen instances there was irregularity varying from an occasional extrasystole to marked irregularity in force and rhythm. Two cases were noteworthy for rapid changes in the quality and rate of the pulse. I lay no emphasis on a small, low-tension pulse because these changes are more probably due to abnormalities in the vasomotor control than to cardiac changes.

In three cases the first sound is described as approaching the second in quality and the intervals between the two sounds as of even duration.

Two cases showed marked gallop rhythm and three embryocardia. The heart sounds are described as feeble and muffled in four cases. The first sound at the apex as unusually feeble twice, as of a murmurish quality twice, as of an indefinite quality once and markedly reduplicated twice. A blowing systolic murmur was heard at the apex in eight cases. In six it was present on admission, the patients being admitted on the fifth, eleventh, (two cases), fourteenth, sixteenth and forty-second day of the illness; in two of these it was absent upon subsequent examination. In two instances the systolic murmur developed while the patients were under observation. The second pulmonic sound was markedly accentuated in four instances.

One patient had marked dyspnea but at autopsy there was edema of the lungs and pleural effusion.

These are in the main the symptoms that are usually described. Huchard lays particular emphasis on the ominous significance of embryocardia. The tendency of the two sounds to approach one another in quality, and of the intervals to become more nearly equal is the first stage of approaching embryocardia. The feeble indefinite first sound at the apex is the beginning of the development of a systolic murmur.

More than one of these symptoms were present in many cases and indeed in a few the circulatory symptoms were so prominent that they may well be classed in the "forme cardiaque" of typhoid fever described by the French authors. Two very characteristic cases are the following:

#### FIRST CASE

Series No. 9. Medical No. 16215. Male medical student, aged 25, white, American, admitted to the Hospital Oct. 2, 1903; died Oct. 15, 1903.

*Present Illness.*—The patient was brought to the hospital in a very collapsed condition; was deeply intoxicated and very dull. No definite history of his illness could be obtained. Patient had left home for college on September 14, and was then not in his usual spirits, apparently not very well. He returned to the city on October 1 in a very exhausted condition, with high fever and delirium. No detailed account of the symptoms during the preceding two weeks could be obtained. After reaching home he was put to bed, and typhoid fever was diagnosed by the family physician from a positive Widal reaction. The following note was made on October 3 by Dr. McCrea:

*Examination.*—"Patient looks deeply intoxicated; mental condition dull, and at times some wandering. Tongue dry. Mucous membranes good color. Slight tremor of lips. Percussion note clear throughout, rather hyperresonant. Breath sounds everywhere heard, accompanied by medium dry râles. Point of maximum impulse in the fifth interspace. Relative cardiac dullness begins at third rib; does not go to right of sternum. Heart sounds clear throughout, first sound much like second. Pulse 30 to the quarter, fair volume, markedly dicrotic, right larger than the left. Abdomen is natural. Numerous rose spots. Respiratory movements well marked. Walls soft and no tenderness. On attempting to feel the spleen there is some rigidity, although spleen is palpable. Relative hepatic dullness begins at the sixth rib and extends 11.5 cm. in the right mammary line." Hemoglobin 80 per cent.; leukocytes 5,000.

*Course of Disease.*—October 4. Note by Dr. McCrea: "Active delirium still continues. Tongue still dry. Everywhere marked capillary stasis. Pulse 30 to the quarter, small volume and rather running. Heart sounds clear; first much like the second. Abdomen is not distended. Everywhere some rigidity. No pain."

October 5: Patient still delirious, muttering and talking continually. Marked subsultus tendinum. Rigidity of the neck, and head is held somewhat retracted. All the extremities are stiff and rigid, and there is a doubtful Kernig's sign. Again the note is made that the first heart sound is of the same quality as the second. The pulse still 30 to the quarter, small and running.

October 6: Patient's general condition not improved. Marked gallop rhythm at the apex and reduplication of the second sound at the base.

October 7: Still marked rigidity of the neck. An occasional drop in the pulse-rate.

October 9: The following note by Dr. McCrea: "Patient's general condition much improved. Active delirium still, although not as marked. Pulse stronger and of better volume. Blood-pressure has risen 20 mm. of mercury since yesterday afternoon. Rigidity of the neck and extremities not so marked. Abdomen not held so rigid. Slight degree of tympanites. No tenderness."

October 13: Swelling noted under both submaxillary regions, apparently involving the glands, and more marked on the left than on the right. Swelling has come on with great rapidity. The parotid glands are not involved.

October 14: The following note was made: "Patient had a very uncomfortable night, owing to salivation and difficulty in breathing. The swelling of the

neck was decidedly more apparent at 11 than at 7 o'clock, especially on the left side, where it extended to the parotid region. Redness and heat extended down over each clavicle. Posterior cervical glands are decidedly larger. A small abscess over the occiput was incised and about 10 c.c. of pus escaped. The patient was delirious, requiring morphin. Pulse fairly good. Leukocytes at 8:30 a. m. were 16,000. Patient is decidedly easier this morning. Swelling less marked. The respirations are easier. Cultures from abscess show *Staphylococcus pyogenes aureus*."

October 15, 1:30 a. m.: There is the following note: "Patient had been very restless during early part of the night, tossing about from side to side in the bed. Breathing was less labored. Swelling of the neck less pronounced. Apparently there was slight fluctuation in the left submaxillary region, with a suggestion of pointing. Discharge from the nostril continued as before. Mind was totally impaired. Although usually quiet, with eyes wide open, at times patient struggled to get out of bed. Abdomen seemed natural. At about 12:45 a hypodermic of morphin, grain  $\frac{1}{8}$ , was administered. Respirations became more rapid and shallow, but never labored, and pulse suddenly fell. A hypodermic of digitalin, gr. 1/30, and strychnin, gr. 1/30, was administered. I was summoned, and on arrival, three minutes after, pulse was not perceptible at the wrist. Heart impulse could not be felt at the apex. There were a few spastic movements; no cyanosis; and patient was dead."

*Clinical Diagnosis*.—Typhoid fever, cellulitis of the neck (angina Ludovici).

#### AUTOPSY

Pathological No. 2192. Autopsy Oct. 15, 1903, at 2 p. m., by Dr. MacCallum.

*Anatomical Diagnosis*.—Typhoid fever, swelling and ulceration of Peyer's patches and solitary nodules, acute splenic tumor, bronchopneumonia, emphysema, atelectasis, arteriosclerosis of aorta and coronaries, acute vegetative mitral endocarditis, phlegmonous inflammation of muscles of the base of the tongue.

The body is that of a fairly well-nourished man, 180 cm. long. The thorax is slightly deformed, the left side being prominent. The neck laterally below the ears is markedly swollen. Rigor mortis and livor mortis are well marked. Over the back there are numerous furuncles. The mucosa are very pale. Subcutaneous fat is small in amount. The peritoneal cavity contains a clear fluid, small in amount. The surfaces are smooth. The ileum, in its lower portion shows many dark areas which apparently correspond with ulcers. Mesenteric lymph-glands are much enlarged. There are very much enlarged lymphoid glands in the omentum and retrosternal tissue.

*Thorax*.—Lungs are voluminous and meet in the middle line. Pleural cavities are free from accumulation of fluid. No adhesions over the lungs. The pericardium contains about one liter of clear yellowish fluid. Pulmonary arteries contain only fluid blood.

*Heart*.—Weight 320 gm. The heart is not enlarged. The surfaces are generally smooth. Epicardium over the right heart is somewhat thickened and opaque. There are a few minute hemorrhages. The right auricle contains post-mortem clot. The tricuspid valve is normal. The pulmonary valves are delicate. The mitral orifice is about normal in size. Along the line of closure of the anterior segment of the mitral valve there are numerous translucent vegetations. The aortic valves are clear. The heart muscle is rather soft, opaque and gray. There are scattered everywhere numerous more opaque, distinct gray flecks or spots. The anterior and descending branches of the coronary artery show numerous yellow flecks of sclerosis. These are of small size, from 1 to 2 mm. in diameter. Almost the whole of the intima is converted into irregular yellowish gray patches which

are not much elevated. The walls of the smaller branches are also thickened. The aorta shows only a very slight thickening, just above the valves. In the wall of the left ventricle near the auriculoventricular ring there are a small number of patches in which the muscle is completely replaced by a grayish white, somewhat translucent fibrous tissue. Two patches of this sort are found measuring 5 mm. in diameter. One or two minute hemorrhages are also found in the substance of the heart muscle.

*Lungs*.—The left lung is very voluminous and cushiony, except in the lower posterior portion of the lower lobe. There the surface is shrunken and the lung substance is airless and of a deep purple color. The bronchial glands are somewhat enlarged. The bronchi contain frothy fluid. The large arteries at the hilum of the lung are clear. The branches flowing into the collapsed area show no alteration. On section, the anterior portion of the lung is generally air-containing, but there are scattered everywhere and especially through the lower lobe minute foci of consolidation with hemorrhages, arranged in small groups. In the posterior portion there is also a number of such areas. The atelectatic part of the lung is very superficial. The right lung is also very voluminous. It is everywhere cushiony. There are over the base areas in which the pleural gloss is lost. The large vessels are free from thrombi. On cut section the upper lobe is found almost everywhere to be air-containing. In the lower lobe foci of consolidation are thickly scattered as in the left lung. Throughout the lungs the alveoli are very large.

*Spleen*.—Weight 300 gm.; slightly adherent to the diaphragm and surrounding areas; has a brownish red color. The capsule has a rough, dry appearance and is covered with fibrin. There are numerous minute hemorrhages. The consistency is greatly decreased. On section the swollen splenic substance is extremely soft and pasty. Numerous hemorrhages throughout. The Malpighian bodies are enlarged and irregular.

*Neck Organs*.—The epiglottis and tissues about the larynx are edematous. The left lobe of the thyroid is much larger than the right. The trachea shows no abnormality. In the tissue about the hyoid bone, especially on the left side, there are numerous small abscess-like foci scattered throughout the muscle, which feels firm and has a translucent appearance. On removing the tongue from the mouth, it is found that in the neighborhood of the left sublingual salivary gland there is an abscess cavity about 1.5 cm. in diameter, containing yellowish pus.

*Liver*.—The surface is smooth and rather grayish. Small points of opacity show throughout the capsule. On the surface the lobules are quite well marked out. They have a gray periphery and dark red center. There are no definite areas of necrosis to be seen. The mucosa of the jejunum is normal in appearance. The gall-bladder is greatly distended. The bile flows freely through the bile ducts.

*Pancreas and Adrenals*.—Normal.

*Kidneys*.—Cortical substance is opaque and swollen. Numerous minute hemorrhages over the cortex. Numerous hemorrhages in the mucosa of the pelvis, which contains cloudy, bloody fluid.

*Intestines*.—Peyer's patches are swollen and have a pitted appearance, with loss of substance. Near the ileocecal valve the swelling is much more extensive, but there are no very deep ulcers and loss of substance is quite superficial. In the cecum the solitary nodules appear superficially ulcerated.

*Aorta*.—The aorta shows beginning sclerosis about the intercostal arteries. Along the aorta there are numerous large hemorrhagic lymph-glands. There are small hemorrhages in the tissue.

## DESCRIPTION OF SECTIONS

The heart muscle shows very extensive parenchymatous and interstitial changes. The fibers everywhere look granular. The "cement lines" are rather prominent and in some places there is a little separation, but there is no marked fragmentation. In some areas the striation of the cells is very indistinct and in others seems entirely absent. Many of the muscle fibers show marked vacuolization on longitudinal section. The nuclei are much swollen and vesicular. Some of the nuclei are large empty bags, although, in most, irregular strands of chromatin are preserved. There is no marked pigmentation of the perinuclear spaces. The spaces themselves are often greatly increased in size. On cross-section in some areas there is very extensive change in the appearance of the fibers. The sarcoplasm is greatly increased in amount; the fibril bundles are diminished in size and number and, in some of the cells, form only a circle about the periphery. Throughout the various sections there are numerous areas of interstitial infiltration. Many of these begin under the epicardium and dip down in between the muscle cells. All of the connective tissue spaces throughout the heart are more richly cellular than is normal. The cells in these areas consist mostly of small mononuclears with, however, many large mononuclears and some polymorphonuclears. There are, too, numerous large cells with round or oval nuclei and of deep eosin-staining protoplasm. Some of these cells exhibit phagocytosis. In several areas there is marked degeneration of the muscle fibers without any apparent interstitial infiltration. In these areas the muscle bundles are filled with a granular material studded with muscle fibers which are diminished in size and have lost their characteristic striation. In one place there is a large area where the muscle fibers seem to have disappeared completely. There is marked periarteritis of one of the large branches of the coronary artery caught in the section.

The papillary muscles are particularly the site of both parenchymatous and interstitial lesions. Many of the smaller vessels show marked thickening of their walls, and in a few the lumen seems completely occluded by cells of the same character as those which have infiltrated the muscle. There is in places marked edema of the connective tissue between the muscle fibers. About some of the areas of infiltration there seems to be a formation of fresh connective tissue.

## SECOND CASE

Series No. 15. Medical No. 15015. Male physician, aged 25. Admitted to the hospital on Nov. 8, 1902, died Nov. 25, 1902. Clinical diagnosis, typhoid fever, hemorrhage.

*History.*—The family history contains nothing of importance. The patient had measles at the age of 21, mumps at the age of 23 and chicken-pox at the age of 24; otherwise, he was always strong and healthy.

*Present Illness.*—On November 2, the patient was taken with headache, general malaise, pain in the back and limbs. These symptoms continued, and on November 5 he had fulness of the neck with marked pain. On the 6th, he had hot and cold flushes, lost his appetite and on the 7th developed nausea. Bowels were constipated. Temperature had ranged from 101 to 102 the two days preceding admission to the hospital.

*Examination.*—On the morning after admission—November 9—Dr. McCrea made the following note: "Patient is well-nourished and robust. Sensorium clear. Tongue very lightly coated, gums and mucous membranes good color. Thorax large and well developed. Expansion good and equal. Percussion note clear throughout. Breath sounds everywhere clear. Heart: point of maximum impulse neither visible nor palpable. Apex by stethoscope in the fifth interspace



7.75 cm. to left of the mid-sternal line. Area of dullness is not increased. Heart-sounds clear throughout. Pulse 24 to the quarter, full and good volume, diastolic. Abdomen is natural. Respiratory movements well marked. No definite rose spots, although there are a few suggestive ones. No especial tenderness. Some gurgling in the right iliac fossa. Liver dullness in the right mammary line begins at the sixth rib and extends about 4 cm. Spleen is not felt."

*Course of Disease.*—After admission, patient's temperature was very high and he showed no response to the tubs. There was considerable nausea and some vomiting. Pulse remained good.

November 13: It is noted that patient is very stupid and dull. Definite rose spots are present on the abdomen. The pulse remains good in quality, but both the respiration and the pulse-rate show variations from time to time.

November 19: On this day, following a sudden drop in the temperature, a little blood appeared in the stools. The amount, however, was too small to have caused the sudden drop. The following note was made by Dr. McCrea: "The patient is dull and drowsy. Tongue somewhat dry and tremulous. Thorax is clear on auscultation and percussion. No abdominal features. No distention or tenderness, and the respiratory movements are well marked. When seen at 11 p. m., the general condition was not so good. The pulse was more rapid and of poorer quality." Later in the day this note was made: "Since last night the patient's general condition has not been so good. He is more delirious and looks worse. Pulse-rate has been irregular and volume poorer. Tongue is dry and tremulous. At times a low, muttering delirium. No subsultus. Respirations are rapid and vary much in rate. Lungs are clear throughout on percussion and auscultation. Heart-sounds are clear. The pulse-rate varies from 128 to 150. Slight change in tension. The abdomen is flat. Respiratory movements well marked. No tenderness, rigidity or muscle spasm." At 11 p. m. it is noted that the pulse is 108 to 112 and of decidedly better volume.

Patient's condition the following morning was somewhat improved, but in the afternoon he again became worse and developed some hiccough. At 11 p. m. the following note was made by Dr. Osler: "Marked stupor and hebeticude. Respirations at times almost normal. Pulse 120, varying both in force and rhythm. Abdomen is soft. Respiratory movements present. No tenderness on palpation."

The following day the patient had considerable hiccough and occasional vomiting. Pulse was slower and of better volume. An enema brought away some changed blood.

November 24: At 4 p. m. the following note was made: "Patient had a sinking attack at 2:20 p. m. Pulse became very rapid, 150, and was weak. There was marked cyanosis. Respirations 13 to the quarter. Patient did not respond to questions. Was stimulated heavily and received a one-liter infusion of salt solution. Rallied somewhat. Maximum blood-pressure 78 mm. of mercury. Pulse-rate 144. Ears very cyanotic." At 10 p. m. the patient's condition was described as very grave. It is noted that the heart-sounds are rather better than the pulse. The attack of the afternoon is characterized in the notes as an acute cardiac break-down. From this attack the patient never completely rallied.

November 25: At 1 a. m. there is this note: "The patient is decidedly worse. Quite unconscious. Respirations over 60. Pulse cannot be felt at the wrist. Heart-sounds are not heard, owing to the rapid, noisy respirations." After this the patient gradually sank and died at 2:10 a. m.

#### AUTOPSY

Pathological No. 2033. Autopsy Nov. 25, 1902, at 8:30 a. m., by Dr. MacCallum.

*Anatomical Diagnosis.*—Typhoid fever, deep ulceration in small intestine, limited ulceration in the colon, acute splenic tumor, general enlargement of the

mesenteric lymph-glands, cloudy swelling of the liver and kidneys, bronchopneumonia, beginning arteriosclerosis, myocardial degeneration, occlusion of pulmonary arteries by cell masses.

*Abstract of Autopsy Notes.*—Body of a fairly well-built man, 178 cm. in length, moderately emaciated. No edema. Slight livor mortis. Rigor mortis well marked. Abdomen not distended. Muscles very red. Peritoneum dry. Mesenteric glands greatly enlarged, dark purplish in color; the tissue overlying them deeply injected. Considerable injection of the peritoneum throughout, especially over the colon and small, red patches of subperitoneal hemorrhage. Intestines nowhere greatly distended.

*Thorax.*—Lungs are quite voluminous, but do not meet in the mid-line. Pleural cavity is free from adhesions and from excessive fluid. Pericardium contains no excess of fluid.

*Heart.*—Weight 250 gm.; is everywhere smooth. Right ventricle is rather soft and flabby. Over the surface of the right ventricle is a tendinous patch rather poorly outlined. Left ventricle is quite firm and mottled in places. Tricuspid and pulmonary valves are delicate. The auricular appendage contains soft clots. The left auricle also contains a soft clot. The mitral valve is delicate. The heart muscle on the left side is opaque, grayish in color, soft, the least touch on cut surface leaving a permanent impression. The heart muscle shows some points and lines of yellowish opacity, but on the whole is rather grayish pink and opaque. The aortic valves are delicate. There is beginning arteriosclerosis at the root of the aorta and there are one or two patches on the ventricular surface of the mitral valve. There are numerous patches of yellowish sclerosis along the coronaries, especially the anterior descending branch. The posterior branch also shows extensive sclerosis. The patches are small and discrete and in large part translucent, flecked with yellow. Tangential sections of the heart muscles show everywhere the same dull opacity with only indefinite flecks of more yellowish color.

*Lungs.*—Voluminous, injected and of a deep red color. Several infarcts throughout the right lung and one particularly large one in the upper portion of the left lower lobe.

*Spleen.*—Tense, rather soft and flabby and contains a few small hemorrhages under the capsule. On section the Malpighian follicles are large and irregular. The pulp is red and greatly swollen.

*Liver.*—Pale and rather pasty. A few small hemorrhages over the left lobe. On section the lobules are well defined with yellowish centers and more red peripheries. The whole liver has a yellowish tint.

*Gall-Bladder.*—Distended with dark green bile. The bile-duct is patent.

*Stomach.*—Numerous small erosions on the lower curvature. The mucosa rather hyperemic.

*Intestines.*—Solitary follicles in the colon are visible, but not greatly swollen. The upper portion of the colon very hyperemic, and as far as the cecum there are several small, quite deep ulcers. Above the ileocecal valve there are four or five large, deep, ragged ulcers with slough adhering to the exposed musculature. Above this, for some distance, all of Peyer's patches are involved, many of them swollen with beginning slough; in others the ulcers extend deep into the muscle. Higher up, swelling is the main feature. There is general hyperemia of the small intestine.

*Pancreas.*—Normal.

*Kidneys*.—On section the whole kidney is rather pale, cortex somewhat swollen. Striations regular and straight. Glomeruli prominent. Labyrinthine portion is swollen and somewhat opaque. Pyramids are pale.

*Aorta*.—Shows delicate patches of sclerosis throughout its whole course. These are narrow, stringy patches in which the yellow opacity is centrally placed.

#### DESCRIPTION OF SECTIONS

The marked granular and fatty degeneration of the fibers which the gross description of the heart indicates are not apparent in the sections. The fibers have a granular appearance and the striation is in places obscured. The "cement lines" are prominent and there is some fragmentation. The nuclei are swollen and the perinuclear spaces enlarged, with some pigmentation at the poles. The sarcoplasm is somewhat increased in amount and on cross-section the fibril bundles are rather widely separated, but the change is not marked. All of the blood-vessels contain more leukocytes than normal, and there is a diffuse scattering of cells throughout the interstitial spaces, but no localized intense areas of infiltration. A branch of the coronary shows well-marked endarteritis. There is no noteworthy change in the small arteries.

These two cases, although so similar in their clinical course, present anatomically widely different conditions. In the first the parenchymatous and interstitial lesions are more marked than in any other heart in our series, and the acute inflammatory changes in the coronaries equally striking. In the second, while the cardiac muscle is soft and opaque with lines of yellowish opacity, the microscopical examination of the fixed tissue shows surprisingly few fiber and no extensive interstitial lesions. The fixing, of course, has obscured the granular and fatty degeneration, which must have been marked. Sections from three different portions of the left ventricle were studied, so the investigation is not as complete as we would wish it to be. The changes in the coronary arteries are extensive.

Of the forty-one cases the cause of death may be roughly stated to be due to:

	Cases.
Perforation with subsequent peritonitis.....	10
Cholecystitis and peritonitis .....	2
Terminal pneumonia .....	2
Intestinal hemorrhage .....	2
Hemorrhage from mucous membranes of respiratory and digestive tracts (hemorrhagic typhoid).....	1
Severe bloody vomiting .....	1
General staphylococcus septicemia and abscesses.....	2
Following convulsions .....	2
Toxemia .....	14
Sudden collapse .....	5

The term toxemia is an indefinite one but is used for want of a better. It is applied to those cases in which death occurred from the disease without the intervention of any direct complication. The classi-

fication comprises then two groups of cases: first, those in which death occurred, if not as the direct result of, at least concomitantly with, the development of serious complications, twenty-two in number; and second, those in which death occurred directly as the result of the typhoid infection, nineteen in number.

Of the 22 cases in the first group:

0 showed marked circulatory symptoms.

7 showed some circulatory symptoms.

15 showed no circulatory symptoms.

Of the 19 cases in the second group:

11 showed marked circulatory symptoms.

5 showed some circulatory symptoms.

3 showed no circulatory symptoms.

These figures are certainly an indication of the relative importance of circulatory disturbances in the causation of death in uncomplicated cases. In the second group are five cases of patients who died rather suddenly and in whom to all appearances death was due to a sudden failure of the heart.

#### THE RELATION BETWEEN THE CIRCULATORY SYMPTOMS AND THE MYOCARDIAL CHANGES

Of 12 cases in which there were well-marked interstitial and parenchymatous lesions:

In 5 there were definite circulatory symptoms.

In 2 there were less marked circulatory symptoms.

In 5 there were no definite circulatory symptoms.

Of 3 cases in which there were well-marked interstitial but only moderate parenchymatous lesions:

In 1 there were definite circulatory symptoms.

In 1 there were less marked circulatory symptoms.

In 1 there were no definite circulatory symptoms.

Of 12 cases in which there were moderate interstitial but well-marked parenchymatous lesions:

In 2 there were definite circulatory symptoms.

In 7 there were less marked circulatory symptoms.

In 3 there were no definite circulatory symptoms.

Of 2 cases in which there were only moderate interstitial and parenchymatous lesions:

In 1 there were minor circulatory symptoms.

In 1 there were no definite circulatory symptoms.

Of 7 cases in which there were no definite interstitial but well-marked parenchymatous lesions:

In 3 there were definite circulatory symptoms.

In 4 there were no definite circulatory symptoms.

Of 5 cases in which there were no definite interstitial and only moderate parenchymatous lesions:

In 1 there were minor circulatory symptoms.

In 4 there were no definite circulatory symptoms.

While patients with even marked interstitial and fiber lesions frequently show during life no prominent circulatory disturbances, it is rare not to find well-marked anatomical changes when such disturbances are present. While the correspondence between the myocardial changes and the clinical picture are by no means constant, the foregoing summary indicates a close relation. Such variations as occur are well known clinically. The sudden and unexpected deaths during convalescence after a mild and uneventful diphtheria are illustrations. When occasionally the grave lesions anticipated from the symptoms during life are missed, it can only be assumed that the histological picture may not always faithfully express the extent of injury the fibers have sustained. I must also again remark that in some of my cases the area of heart muscle studied was too small to allow of anything like a satisfactory conclusion about the condition of the organ as a whole. What I mean by "circulatory symptom" I have previously explained. They are symptoms which in all likelihood arise from some damage to the heart itself and are not the usual circulatory derangements consequent to vasomotor paralysis. As has been previously noted, five patients died apparently of cardiac failure. All showed definite myocardial lesions and in four the changes were well marked.

One would presume that cardiac lesions would be more common in patients dying of the typhoid infection itself than in those dying after fatal complications, notably after perforation of the intestine or the gall-bladder.

Of the 19 patients dying of "toxemia":

- 7 had marked interstitial and parenchymatous lesions,
- 1 had marked interstitial and moderate parenchymatous lesions,
- 6 had moderate interstitial and marked parenchymatous lesions,
- 4 had no interstitial but marked parenchymatous lesions,
- 1 had only slight parenchymatous lesions.

Of 12 patients dying from peritonitis (10 after perforation of intestines, 2 after perforation of gall-bladder):

- 6 had marked interstitial and parenchymatous lesions,
- 1 had marked interstitial but moderate parenchymatous lesions,
- 4 had moderate interstitial and marked parenchymatous lesions,
- 1 had marked interstitial and moderate parenchymatous lesions,
- 2 had no interstitial but marked parenchymatous lesions,
- 4 had no interstitial and only slight parenchymatous lesions.

Of sixteen cases in which there was irregularity of the pulse, in all but two there were marked parenchymatous lesions and in only three were interstitial lesions entirely absent.

Of the eight cases in which there was a systolic murmur at the apex, in 4 there were extensive interstitial and parenchymatous lesions, in 4 definite parenchymatous but no interstitial changes.

## THE SIGNIFICANCE OF THE HEART MUSCLE CHANGES IN TYPHOID FEVER

In spite of the extent to which the heart muscle is damaged in typhoid fever it is a difficult matter to determine how far the functional capacity of the heart is impaired. Stokes called attention to the frequent lack of correspondence between the severity of the disease or the prominence of circulatory symptoms and the degree of anatomical change in the heart muscle. The most marked lesions are sometimes found when one would least expect them and the lesions are sometimes mild when the clinical course of the disease would lead us to predict their presence. In the section where I have compared the clinical symptoms of the disease and the histological picture of the heart muscle the lack of any constant relation is apparent. It may be that the muscle cells are often more severely injured than one would judge from the structural changes they present and it is indeed remarkable what a high grade of efficiency the heart may preserve in spite of the existence of very extensive fiber lesions. I have, however, noted that where the circulatory symptoms have been unusually prominent and particularly where death has seemed due to sudden cardiac failure, extensive myocardial lesions have almost constantly been present. On the other hand, in some cases in which there were no unusual circulatory symptoms during life, quite as extensive myocardial lesions have been found. Krehl<sup>25</sup> has suggested that the character of the toxin and the position of the lesions may be matters of primary importance. Albrecht<sup>26</sup> has particularly emphasized the significance of the position of the lesion. From his anatomical studies he has attributed great importance to special bands of muscle fibers in the proper coordination of the heart-beat and believes that lesions involving certain areas would produce far greater damage than the same lesion situated elsewhere. Aschoff and Tawara<sup>19</sup> refuse to accept the anatomical conclusions of Albrecht and reject the pathological assumptions based on them. They in turn are particularly interested in lesions which may interfere with the impulse-conducting fibers of the bundle of His. Tawara has previously published an excellent anatomical study of the distribution of this bundle. The effect that lesions in various branches of the bundle may have on the rhythm of the cardiac movements and what effect, if any, they may exercise on the functional capacity of the heart, are questions to be solved. The ramifications of His' bundle are particularly rich just under the endocardium and as areas of cellular infiltration are especially common there, Aschoff and Tawara

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25. Krehl: *Erkrankungen des Herzmuskels*, p. 107.

26. Albrecht: *Der Herzmuskel*, Berlin, 1903.

suggest the association as a possible explanation of the irregularities common in infectious diseases.

It is a much-discussed question how far granular and fatty degeneration impairs the functional capacity of the heart. Clinically in conditions where they are most extensive, as in phosphorus poisoning and anemia, we miss serious circulatory symptoms. Experimentally the lack of relation between the two is even more striking.<sup>27</sup> It is remarkable, too, how large an area of the heart muscle may undergo necrosis without appreciably impairing its function.<sup>25</sup>

Nothing more definite can be said about the significance of fragmentation. There are certainly no characteristic symptoms associated with the lesion as Renaut and Landouzy<sup>28</sup> at first thought. Von Recklinghausen, in 1890, contended that the tears occur as the result of perverse contraction at the moment of death. This view, that the occurrence of the lesion is an agonal event, has been generally accepted. It is assumed that certain areas of heart muscle die a little before others and the contractions of the still living fibers tear them asunder. Still the exact mechanism by which they are torn into so many fragments does not appear clear. The lesion is such a common one and occurs in so many different conditions that no pathological importance can be attached to it.

Changes in the fibrillar structure of the muscle must certainly interfere with the functional activity of the cell but these lesions we have not found extensive enough to assume that so large a number of fibers were affected as to compromise the efficiency of the heart as a whole. Vacuolization and changes in the distribution of the sarcoplasm are lesions no doubt of still graver importance for the life of the cell, but these are no more frequent than the fibrillar lesions.

The changes in the nuclei have given rise to some discussion. Weigert<sup>29</sup> thought the large vesicular forms represent the first stage in division and multiplication and this view has been supported by Oertel.<sup>30</sup> The publications of Ehrlich,<sup>31</sup> Romberg and Krehl leave little doubt, however, that they are distinctive marks of degeneration. Krehl<sup>32</sup> has found changes in the size and shape of the perinuclear spindle of sarco-

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27. Lubarsch and Ostertag: *Ergebn. d. allgem. Path. u. path. Anat.*, 1903, ix, 612.

28. Quoted by Lubarsch and Ostertag: *Ergebn. d. allgem. Path. u. Path. Anat.*, 1903, ix, 612.

29. Weigert: *Samml. klin. Vortr. (Volkmann's)*, 1878, 162-163; quoted by Albrecht: *Der Herzmuskel*, p. 245.

30. Oertel: Quoted by Albrecht: *Der Herzmuskel*, p. 245.

31. Ehrlich: *Charité Ann.*, 1878, v, 198.

32. Krehl: *Erkrankungen der Herzmuskel*, p. 105.

plasm more constantly associated with cardiac insufficiency than any other single lesion. He ascribes great importance to its presence. Aschoff and Tawara are skeptical of the significance of the various fiber lesions described. The nuclear lesions and the increase in sarcoplasm, especially, they believe, are often more apparent than real.

As the nuclei and sarcoplasm represent the essential living structure of the cell, changes in these are of primary importance as concerns its life. A fiber may probably recover and be restored to activity even when granular and fatty degeneration and fibrillar lesions are extensive. Albrecht<sup>26</sup> believes that restitution is possible even when the nuclei show marked vesiculation. When a cell, however, has once died, it is improbable that its place can be filled by newly formed fibers. There is no conclusive evidence of regeneration of cardiac fibers.

From the careful observation of Mollard and Regaud it seems probable that interstitial lesions occur much later than the fiber lesions and that they are seldom present earlier than the end of the second week. As circulatory symptoms when they occur tend to appear during the third week, the inference is near that they have an important bearing on their development. The exact manner in which these areas of interstitial infiltration affect the functional activity of the heart does not seem clear, but the clinical evidence of their significance is indisputable.<sup>33</sup>

Every death during an uncomplicated acute infectious disease is a circulatory death and in every circulatory failure two factors are of importance, the propelling force and the peripheral resistance or the heart and the vasomotor system. What part does the heart and what part does the vasomotor system play in the deaths from acute infections and in the development of the symptoms frequently observed during the course of the disease and during convalescence?

Certain of these symptoms are unquestionably due to alteration in the heart itself. The not infrequent dilatation with relative mitral insufficiency, the cardiac irregularities and the changes in rhythm, notably embryocardia, can have no other origin. The unusually rapid or unusually slow pulse in all probability depends upon myocardial lesions. It is during convalescence that symptoms of cardiac insufficiency make their appearance most clearly. Prolonged irregularity of the pulse, unusually rapid heart action, breathlessness and fatigue on exertion, a persisting mitral insufficiency, occur frequently enough to indicate the extent and importance of the changes the heart muscle has undergone. The tragic sudden death so common during convalescence from scarlet fever and especially from diphtheria is unusual after typhoid and the

33. See particularly Romberg: *Deutsch. Arch. f. klin. Med.*, 1891, xlviii, 369.



greater severity of circulatory derangements in the two former diseases stands in direct relation to the more common and more extensive myocardial lesions that obtain. Still an occasional sudden death and more commonly prolonged invalidism after typhoid attest the importance of the cardiac changes in this disease.<sup>34</sup>

It is difficult to determine the relative importance of the fiber and the interstitial lesions in the development of these symptoms. If Renaut is right in contending that the interstitial changes are but secondary to the fiber damage and their extent dependent on the severity of the parenchymatous lesion, the question has no significance. Those unwilling to accept this position will see in the time of occurrence of the symptoms, towards the end of the disease and notably during convalescence, and in the almost constant association of intense interstitial lesions with severe cardiac manifestations, an important indication. This relation is particularly striking in the sudden deaths after diphtheria. Circulatory symptoms are especially common and grave in diphtheria infections and it is in this disease that the interstitial lesions are most extensive and most striking.

During the height of an infectious disease it is more difficult to determine the relative importance of myocardial lesions and of vasomotor paralysis in the circulatory failure. Here, too, it is probable that sudden and unexpected death is due to cardiac failure and in some cases the symptoms of cardiac disturbance are so striking that we cannot hesitate to ascribe the essential part of the circulatory failure to the myocardial lesions. In the more common types of the disease vasomotor paralysis would seem to be the essential factor. Romberg, Pässler and Burns,<sup>35</sup> from an admirable experimental study, conclude that even when the myocardium is the seat of an extensive lesion it may remain perfectly efficient during the height of the infection, death being then due entirely to vasomotor paralysis. Their methods of investigation cannot be briefly presented nor can the criticisms of von Stejskal, who attempts to discredit their results. Von Stejskal,<sup>36</sup> working in von Bach's laboratory, measured the auricular and the arterial pressures and in their variation

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34. Excellent clinical pictures in Krehl (*Erkrankungen des Herzmuskels*, p. 280); Romberg (*Deutsch. Arch. f. klin. Med.*, 1891, xlviii, 369; also *Krankheiten des Herzens*, Stuttgart, 1906, p. 328); and Leyden (*Ztschr. f. klin. Med.*, 1882, iv, 334).

35. Romberg, Pässler and Burns: *Untersuchungen über die allgemeine Pathologie und Therapie der Kreislaufstörungen bei acuten Infektionskrankheiten*, *Deutsch. Arch. f. klin. Med.*, 1899, lxiv, 652.

36. Stejskal: *Kritisch experimentelle Untersuchungen über den Herztod im Folge vom Diphtherietoxin*, *Ztschr. f. klin. Med.*, 1902, xlvi, 367.

sees direct evidence of circulatory stasis and concludes that the heart must play at least an important rôle in the circulatory failure.

Of the arterial changes in typhoid fever we have been able to make but a limited study. A few cases exhibited endarteritis and periarteritis of the larger branches of the coronaries but the sections could not be used to determine the extent and frequency of the lesions. The extensive changes in the smaller arteries noted by Hayem, and on which he lays so much importance, have been missed by other authors and they are certainly not present in my material. Such arterial lesions as I have found might, however, exert some influence on the immediate outcome of the disease and particularly on the subsequent integrity of the circulatory system. They are, in most cases, hardly extensive enough to interfere seriously with the nutrition of the heart muscle but are important factors in the development of subsequent arteriosclerosis. Thayer has shown that the average blood-pressure of individuals having had typhoid fever is higher than that of those who have escaped it and the radial arteries more frequently thickened. We are coming to ascribe a more and more important rôle to the infectious diseases in the production of chronic arterial changes.

The acute myocardial lesions are also significant for the subsequent well-being of the patient. The destruction of muscle fibers and the large areas of interstitial infiltration leave scars which must influence the future efficiency of the heart. Landouzy and Siredey report a case of death in a second attack of typhoid fever in which they found, besides acute myocardial lesions, old fibrous scars which they ascribe to the first attack, there being no evidence of arterial disease. One of Romberg's scarlet fever subjects showed cardiac scars, which Romberg considers the remains of a previous attack of typhoid fever. Mollard and Regaud have found fibrous areas in the hearts of their dogs, killed a year after treatment with diphtheria toxin.

#### SUMMARY

The anatomical lesions produced by typhoid fever in the heart and blood-vessels have long been known. While there is much diversity of opinion about the extent and frequency of the lesions, their occurrence and importance is unquestioned. In my study of forty-three hearts from patients dying of typhoid fever I was able to find some changes in practically all, although in most the lesions were not extensive enough to allow one to assume with certainty that the efficiency of the heart muscle

was compromised. There is unfortunately no satisfactory evidence at hand to allow one to judge the functional capacity of the heart by the character and extent of the histological lesions and frequently the two seem not to run parallel. In at least six of my cases both the fiber and interstitial lesions are so intense that I could hardly associate their presence with complete efficiency of the organ. I do not find any evidence of wide-spread change in the smaller branches of the coronary arteries but frequently periarteritis and endarteritis in the large and medium-sized branches. No doubt these lesions must in some degree interfere with the nutrition of the heart and are of importance both for the immediate efficiency of the organ and its future integrity.

There are certain symptoms during the course of an acute infectious disease which point directly to the presence of some cardiac lesion and often to cardiac insufficiency, notably irregularities of rhythm, and the physical signs of beginning dilation. Certain sudden deaths can be satisfactorily explained only upon the assumption of abrupt cardiac failure. Romberg has asserted that during the height of an infection the circulatory failure depends entirely on vasomotor paralysis. Even though the vasomotor system plays the important rôle, the work of Stejskal shows that the heart is not always perfectly efficient and that it cannot be entirely disregarded as a factor in the failure. It is during convalescence particularly that the symptoms of a damaged myocardium stand out most clearly. Such symptoms are not nearly so common after typhoid as after other infections, notably diphtheria, but they occur frequently enough to indicate the significance of the damage the heart has sustained.

Undoubtedly these lesions of the myocardium and of the arteries are of the greatest importance for the future health of the individual. We are being more and more deeply impressed with the significance of infectious disease in the production of chronic arterial and myocardial disease. Typhoid fever has not in this regard the same importance as rheumatism, syphilis, or diphtheria, but on account of its prevalence is a factor to be seriously reckoned with. The prevention of infectious diseases will probably prove one of the strongest prophylactic measures against the degenerative lesions of the circulatory system.

21 West Franklin Street.

TABLE OF CASES OF TYPHOID SHOWING CONDITION OF HEART MUSCLE

Pathological No.	Age.	Sex.	Color.	Duration of Illness.	Cause of Death.	Main Clinical Features.
2140	10	F.	B.	18 days.	Toxemia.	Onset abrupt with vomiting and dizziness and marked mental features. Admitted on 7th day of disease. Was deeply intoxicated and had symptoms of meningeal irritation. High fever. Pulse rapid and irregular. Apical systolic murmur developed while child was in hospital.
2300	19	M.	W.	60 days	Peritonitis following intestinal perforation and operation.	Onset indefinite. Had been ill 3 weeks before admission with pain in hip and loss of appetite and general malaise. No special symptoms until 12nd day, when he had a hemorrhage of about 15 c.c. Following this became very dull and deeply intoxicated. On 46th day signs of perforation. Operation. After operation patient remained very stupid and toxic. On 55th day signs of peritoneal irritation reappeared but patient's condition did not permit of a second operation. No definite circulatory or cardiac symptoms except well-marked arteriosclerosis. Heart sounds described as somewhat muffled.
2385	22	M.	W.	35 days.	<i>Staphylococcus aureus</i> septicemia.	Onset with headache and general malaise 4 days before admission. Was irrational and deeply intoxicated on admission. A severe infection. Hemorrhage of 100 to 300 c.c. on 20th and 21st days. On 17th day abscess in thigh opened, followed by a profuse crop of boils. Severe hemorrhage on the 24th day. <i>Staphylococcus aureus</i> cultivated from the blood. No special circulatory symptoms.
2376	22	M.	B.	28 days.	Peritonitis following intestinal perforation and operation.	Onset with chill, fever and headache. Admitted on 6th day. Dull but in good condition. Later patient became irrational and delirious. On 24th day symptoms of perforation and of pneumonia. On 25th day operation on a moribund patient. No circulatory symptoms.
2373	33	M.	W.	46 days.	Peritonitis following perforation.	After an indefinite illness of 5 weeks, the last two having been spent in bed, patient entered hospital. Was very ill on admission and soon became deeply intoxicated. The last five days of life his condition was desperate and on the last two days had a number of small hemorrhages. Perforation was not diagnosed and was probably a terminal event. On admission pulse a little irregular and at end of disease was markedly so. The first sound at apex was dull and muffled.
2252		F.				History lost.
2199	15	M.	B.	22 days.	Cholecystitis with localized peritonitis. Pneumonia; meningitis.	Entered hospital after an illness of 15 days consisting of fever, chills, headache and languor. Was dull and emaciated on admission. Symptoms throughout were those of meningeal irritation. Patient died in coma on 22nd day of disease. Last few days of life had much abdominal pain and tenderness. Pulse showed marked variations in quality and in rate.
2197	43	M.	W.	65 days.	After a prolonged illness died suddenly after being turned over in bed.	After a 5 weeks' illness with chills and fever and diarrhea during which time he had worked almost continuously he entered hospital. During the month patient was in hospital never had a high fever but there was marked prostration. Diarrhea was a prominent symptom. The pulse from admission on was rapid, weak and irregular. For several days when temperature was subnormal pulse remained over 90. Became very weak and died suddenly after being turned over in bed. Abundant albumin in urine.
2192					Cited in the text.	
2184	20	M.	B.	22 days.	Intestinal hemorrhage.	Entered hospital after 3 weeks' illness. Was dull, stupid at deeply intoxicated on admission. The same evening had severe intestinal hemorrhage and died the following day.

# ILLUSTRATING ARTICLE BY LOUIS HAMMAN

Anatomical Diagnosis.	Description of Heart	
	Gross.	Microscopical.
Typhoid fever with hyperplasia and ulceration of lymphoid follicles of small and large intestines. Acute splenic tumor with multiple infarcts. Cloudy swelling of viscera. Marked lymphadenitis of mesenteric lymph-glands with necrosis. Distention of gall-bladder. Pseudo-lobar pneumonia. Acute fibrinous pleurisy.	Somewhat enlarged; weight 200 gm. Pericardium opaque and somewhat thickened, especially along the vessels. Valves normal. Muscle of left ventricle rather pale and cloudy-looking.	The fibers look granular and in some places there is segmentation. The nuclear changes are well marked. No interstitial lesions except in one place under the epicardium there are many large round cells.
Typhoid fever with ulceration of the ileum and colon. General fibrinopurulent peritonitis. Acute splenic tumor. Cloudy swelling of liver and kidneys. Chronic mitral and tricuspid endocarditis. Slight arteriosclerosis. Chronic adhesive pleuritis of left side. Compensatory emphysema of right lung. Healed tuberculous foci in the right lung.	Weight 230 gm. Tricuspid and mitral valves show slight thickening along borders. Muscle rather soft and brownish-red in color. Cloudy on tangential section.	Fibers look granular. On cross-section there is seen an increase of sarcoplasm with contraction of fibril bundles. Some segmentation and fragmentation. The nuclear changes are marked and there is a striking increase in the amount of pigment. Marked chronic interstitial and vascular changes. Some diffuse intestinal collections of cells.
Typhoid fever. General septicopyemia. Miliary abscesses in kidneys and right lung. Atheroma of aorta and coronary arteries. Bronchopneumonia. Typhoid ulceration of the ileum and large intestine.	Rather small; weight 200 gm. Firm. Muscle of a light brown color and a little pale. Quite firm and not friable.	Fibers look swollen and granular. Markings are indistinct. Nuclear changes are well marked and there is considerable pigment. No special interstitial changes.
Typhoid fever. Perforation of cecal ulcer. Fibrinopurulent peritonitis. Bronchopneumonia. Chronic fibrinous pleuritis. Fatty degeneration of liver with chronic perihepatitis. Cloudy swelling and congestion of kidneys.	About normal size, weighing 220 gm. Musculature of left ventricle soft and flabby. On tangential section decidedly cloudy. Fresh sclerosis in aorta and coronaries.	Fibers look granular. Nuclear changes fairly well marked and some pigmentation. Some sections show considerable segmentation. No special interstitial changes. Section of coronary artery shows patch of fresh sclerosis.
Typhoid ulceration with extensive ulceration of the colon. Hemorrhage. Perforation and peritonitis. Bilateral hydrothorax. Bronchopneumonia. Chronic passive congestion of lungs and viscera. Acute splenic tumor. Cloudy swelling of liver and kidneys.	Somewhat increased in size; weight 380 gm. Pericardium smooth and glistening. Musculature of left ventricle considerably hypertrophied. Is firm and of good color but on section appears markedly cloudy. Fresh sclerosis of aorta and coronaries.	Fibers appear granular and on cross-section some increase in sarcoplasm. Nuclear changes are well marked and there is moderate pigmentation. Some segmentation. Definite areas of cells under epicardium which in places dip down between the muscle fibers. The cells are mostly small mononuclear with some polymorphonuclears and many large endothelial cells.
Typhoid fever. Operation (amputation of uterus). Infected abdominal wound. Edema and atelectasis of lungs. Bronchopneumonia. Cloudy swelling of liver and kidneys. Edema and swelling of pancreas. Multiple abscesses of kidneys. Acute splenic tumor. Early arteriosclerosis. Healing ulcers in small intestines.	About normal in size. Muscle pale, anemic and rather cloudy. The tissue has a yellowish color, especially marked in the papillary muscle.	Fibers are rather granular. Some increase of sarcoplasm. Nuclear changes well marked. Moderate fragmentation. No special interstitial lesions.
Typhoid fever. Swelling and ulceration of Peyer's patches and solitary nodules. Bronchopneumonia. Acute cholecystitis with ulceration and localized peritonitis. Acute cerebrospinal meningitis.	Slightly larger than normal. Muscle rather flabby and slightly mottled in appearance but not markedly opaque. Fresh sclerosis of aorta and coronary.	Fibers a little granular. Nuclear changes not marked. One section shows slight fragmentation. No definite interstitial changes.
Typhoid fever. Ulceration of ileum and colon. Marked consolidation of lungs with gangrene. Cirrhosis of the liver. Chronic diffuse nephritis.	Not enlarged. Sclerotic patches on back of anterior mitral leaflet and at root of aorta. Muscle is grayish pink in color and rather soft. On tangential section somewhat mottled and opaque.	Some fibers look granular. Moderate fragmentation. Nuclear changes well marked but not extensive. Considerable pigmentation. Many areas of accumulation of small round cells under epicardium but no invasion. Throughout the connective tissue spaces the cells are unusually numerous but no areas of marked infiltration. Some of the artery walls show a chronic thickening.
Typhoid fever. Hyperplasia and ulceration of lymphatic structures of small and large intestines. Hemorrhage into bowel from cecal ulcer. Cloudy swelling of liver. Acute nephritis. Acute splenic tumor.	Weight 280 gm. Normal in size. Muscle pale and somewhat soft. Slight sclerosis at base of aorta.	Fibers look granular. In some the longitudinal striation is obscured. Some vacuolization. On cross-section some increase of sarcoplasm. Marked nuclear changes with pigmentation. Marked segmentation. Capillaries unusually full of leukocytes. Several areas of considerable interstitial infiltration. Many large and small round cells and a few eosinophils.

TABLE OF CASES OF TYPHOID SHOWING CONDITION OF HEART MUSCLE

No.	Age.	Sex.	Color.	Duration of Illness.	Cause of Death.	Main Clinical Features.
48	31	M.	W.	18 days.	Toxemia.	Was so ill on admission to hospital could give no history. Sister says he had been ill for a little over 2 weeks with fever, diarrhea and blood in stools. On admission he was stupid, sallow and emaciated. Pulse was rapid and irregular and there was a loud systolic murmur at apex with some accentuation of pulmonary second sound.
91	31	M.	B.	18 days.	Toxemia.	Onset 2 weeks before admission with headache and fever. Was very ill on admission; dull and irrational. Became extremely intoxicated and died 4 days later. Pulse was small and fast. Heart sounds muffled. Pulmonic second sound accentuated. Marked gallop rhythm for 1 day before death.
66	17	M.	W.	17 days.	Peritonitis following intestinal perforation.	Taken ill 10 days before admission with headache, chill and fever. On admission was very ill and dull. Became actively delirious and on the 7th day had perforation, followed by operation and death. No circulatory symptoms except a soft systolic murmur at apex and over body of heart.
52	32	M.	W.	3 months.	Exhaustion, suddenly.	Death came rather A most unusual clinical course. Entered hospital after 1 week's illness with headache, malaise and fever. On the 27th hospital day temperature reached normal only to start off again on an intercurrent relapse. During this relapse the patient's condition was worse than during the original illness. He looked ragged and fever-eaten. After 2 months of fever the temperature reached normal. Remained normal for 15 days during which patient improved, then started up again, and patient died, wasted and worn, 38 days later. The only notable circulatory symptom was an unusually rapid pulse. During the intercurrent relapse he had several sinking spells, in one the pulse going to 160. At this time, too, heart-sounds had a tendency toward embryocardia. At the end death came suddenly.
29	28	F.	B.	3 months.	Cited in the text. Exhaustion; toxemia.	Entered hospital after having been ill for 3 weeks with chills, fever, nausea and vomiting. Was extremely ill on admission and it seemed probable that she would die at any time. On 31st day in hospital had a sudden drop in temperature followed by four chills in the next few days. On the 9th day pneumonia developed. On the 41st day developed a cellulitis back of left ear. From 33rd day on fed almost entirely by stomach-tube. Toward the end there was marked abdominal distention due to acute dilatation of the stomach. Anemia was a prominent feature on admission and throughout the illness. The pulse was unusually rapid and at times a little irregular. Heart-sounds are described on one occasion as approaching embryocardia; on another that the first sound is reduplicated.
91	21	M.	B.	32 days.	Toxemia.	Entered hospital on 9th day of illness. Was deeply intoxicated and very ill on admission. Became delirious and then very dull. For 2 days before death was lethargic. Considerable albumin in urine. No special cardiac or circulatory symptoms. Pulse described once as being a little irregular in force. Soft systolic murmur over body of heart.
945	5	M.	W.	7 weeks.	Toxemia.	Ill for 6 weeks before entering hospital. On admission was desperately ill with marked meningeal symptoms. Typhoid bacilli obtained from spinal fluid although there was no meningitis at autopsy. Pulse was very rapid and weak. Embryocardia. No murmurs. Died 6 days after admission to hospital, the meningeal symptoms persisting to the end.
907	29	M.	W.	26 days.	Peritonitis following perforation	Was taken acutely ill 3 weeks before admission with fever and general malaise. Was in good condition on admission. After 9 days in hospital had several hemorrhages, amounting in all to about 1 liter. On the 11th day perforation followed by operation. Stood operation well but following day developed hiccup and died on the 12th day. No special circulatory symptoms.
890	17	F.	W.	22 days.	Cardiac failure.	A very severe attack of typhoid fever. Admitted on 11th day of illness in a very grave condition and during whole time in hospital was desperately ill. Was highly excitable and delirious and finally stuporous. Death followed several hours after a collapse apparently due to cardiac failure. On admission it was noted that first and second sound were alike in quality and later there was embryocardia. Pulse was irregular for 4 days before death.

# ILLUSTRATING ARTICLE BY LOUIS HAMMAN

## Anatomical Diagnosis.

## Description of Heart.

### Microscopical.

### Gross.

typhoid fever. Swelling and ulceration of Peyer's patches and solitary follicles. Retroperitoneal hemorrhage. Cloudy swelling of heart, liver and kidneys. Acute splenic tumor; swelling of mesenteric lymph-glands. Arteriosclerosis.

Muscle of medium firmness. Pale red color. On tangential section shows a number of small yellowish spots and a few minute hemorrhages. Papillary muscles show some hemorrhages.

Marked vacuolization of fibers, especially on cross-section. Some segmentation. Nuclear changes are particularly marked and there is extensive pigmentation. All the connective tissue spaces are richly cellular and there are numerous areas of considerable infiltration. Both the fiber and interstitial lesions are quite well marked. Fibers show no marked changes. Nuclei are large and vesicular but not extensively so. Some increase of sarcoplasm. No segmentation. Some small round cells throughout the connective tissue strands but no large areas and no infiltration.

typhoid fever. Ulceration of colon and of small intestine. Cloudy swelling of liver and kidneys. Bronchopneumonia. Hemorrhagic infarction and edema of lungs.

Not enlarged. Epicardium in places thickened and white. Muscle of right ventricle flabby and soft. Muscle of left ventricle rather gray and somewhat opaque but shows no distinct patches of fibrous tissue.

Sections show very few changes. Some nuclei are moderately swollen and the perinuclear space enlarged. Some "cement lines" are visible. Capillaries are rather full. No interstitial infiltration.

abdominal operation wound. Typhoid fever. Ulceration of ileum and cecum and mucosa of appendix. Perforation of ulcer in ileum. General peritonitis. Abscess formation in both lungs. Bronchopneumonia; fibrinopurulent pleurisy.

Not enlarged. Fairly firm in consistency. Muscle gray and rather soft. Homogeneous in appearance. No evidence of fatty change.

Very extensive nuclear changes. Greatly swollen and perinuclear spaces much increased. Some fibers show vacuolization. On cross-section well-marked and widespread increase in sarcoplasm. Some segmentation. Many small areas of cellular accumulation throughout the interstitial tissue and notably about the blood-vessels. No infiltration from these areas. Some chronic fibroid patches. Arteries show some chronic thickening.

typhoid fever. Fresh and healing ulcers in the colon. Hyperplasia of the lymph-glands. Acute splenic tumor. Bronchopneumonia. Typhoid ulcers in the appendix. Focal areas in the liver.

Not enlarged. Surface smooth. Muscle somewhat soft. On section not homogeneous but shows opaque yellow patches scattered here and there. Root of aorta shows a few small patches of beginning sclerosis. Several patches of fresh yellow sclerosis in coronaries.

typhoid fever. Healed ulcers in the intestines. Dilatation and displacement of stomach. Encapsulated fibrinopurulent pleurisy. Bronchopneumonia. Chronic proliferative pelvic peritonitis. Fatty degeneration of the myocardium.

Weight 250 gm. Superficially everywhere smooth. Muscle rather grayish. Soft and flabby, and fairly homogeneous. On tangential section shows a uniform grayish opacity. In papillary muscles some opaque yellowish specks and a close inspection of their endocardial surface shows the mottling characteristic of fatty degeneration.

The nuclear changes are well marked. The fibers look a little granular. The perinuclear spindle is enlarged and there is moderate pigmentation. Marked fragmentation. Beneath the epicardium numerous collections of cells which dip down between the muscle bundles. Small areas of cellular accumulation throughout the section. Cells are mostly small mononuclears, but there are many polymorphonuclears and some large mononuclears.

typhoid fever. Multiple ulcers in jejunum, ileum and large intestine. In small intestine ulcers are sloughing; in large are confluent and diphtheritic. Enlargement of retroperitoneal and mesenteric glands. One suppurating gland. Fatty degeneration of heart muscle. Great emaciation. Bed-sore. Acute bronchopneumonia.

Weight 200 gm. Normal size. Muscle pale and yellowish-brown in color. Consistency soft.

Fibers do not show the marked fatty degeneration described in gross specimen. Look granular but striation well preserved. Some fragmentation. Nuclear changes marked. Some fibers show vacuolization but this change not marked. Some scattered cells throughout the interstitial tissue but no definite interstitial infiltration. In spite of the extreme softness of heart muscle the microscopic lesions are not especially striking. Moderate nuclear changes with some pigmentation. Considerable sarcoplasmic increase. Slight fragmentation. Collections of small round cells under epicardium and about blood-vessels but no tendency to infiltration. Fiber changes are definite but not striking. Extensive fragmentation; some nuclear change and a little pigmentation. No marked increase in sarcoplasm. Fibers appear granular. Hemorrhage between fibers. Collections of small and large round cells about blood-vessels but no interstitial infiltration.

typhoid fever. Swelling and ulceration of Peyer's patches with scough formation. Hyperplasia of lymph-glands and spleen. Focal necroses of liver. Bronchopneumonia.

Weight 80 gm. Pericardial layers edematous. Heart extremely soft and flabby. Muscle has a watery appearance, grayish-yellow in color. The organ is excessively soft and collapses in the hand.

typhoid fever. Operation wound. Suture of perforated intestine. Diffuse peritonitis. Emphysema of all organs (gas bacillus).

Weight 380 gm. Epicardial surface smooth. Coronary arteries filled with gas. Muscle extremely soft and flabby. Has a gray granular appearance on section.

Fiber changes are definite but not striking. Extensive fragmentation; some nuclear change and a little pigmentation. No marked increase in sarcoplasm. Fibers appear granular. Hemorrhage between fibers. Collections of small and large round cells about blood-vessels but no interstitial infiltration.

typhoid fever. Sloughing ulcers in the ileum and colon. Distention of intestines. Hyperplasia of mesenteric lymph-glands. Acute splenic tumor. Lobar pneumonia. Acute serofibrinous pleurisy.

Weight 220 gm. Surface smooth. Muscle fairly firm and of a uniform brownish-red color.

Slight fragmentation. Nuclear changes moderate. Some sarcoplasmic increase. About blood-vessels and throughout interstitial bands small collections of small and large round cells. No definite interstitial infiltration.

TABLE OF CASES OF TYPHOID SHOWING CONDITION OF HEART MUSCLE

Pathological No.	Age.	Sex.	Color.	Duration of Illness.	Cause of Death.	Main Clinical Features.
1884	19	M.	B.	11 days	Peritonitis following perforation.	Onset 5 days before admission to hospital with fever, headache and stiff neck. In good condition on admission but temperature was high. On 6th day developed abdominal pain. Abdominal symptoms became more marked and patient died on 9th hospital day.
1827	42	M.	W.	34 days	Toxemia. Hemorrhagic typhoid.	Admitted after having been ill nearly 4 weeks with chills and fever and headache. On admission was sallow and emaciated and very ill. Developed numerous hemorrhages into skin and had blood in stool and sputum. Became very dull and stupid and the last few days of life had marked dyspnea. Heart sounds were faint and distant. Pulse markedly irregular the last 10 days. Radial arteries considerably thickened.
1806	33	F.	B.	Indefinite	Died in coma after convulsions.	Patient very ill when she entered hospital. Shortly after admission had a number of severe convulsions, passed into coma and died 7 hours after. Clinically the case was considered to be uremia and a correct diagnosis was made only at autopsy. The history given was that patient was taken suddenly ill with a sharp chill 5 days before admission. No cardiac symptoms made out but the examination was not satisfactory.
1786	38	F.	W.	22 days	Peritonitis following cholecystitis and perforation of gall-bladder.	Patient admitted to hospital dull and ill after 2 weeks of fever, headache and diarrhea. On admission had pain and tenderness in right hypochondrium. Signs of peritonitis became more and more prominent. No special circulatory features.
1774	32	M.	W.	13 days	Toxemia.	Taken ill 12 days before admission with fever and general constitutional symptoms. On admission was irritable and stupid. Pulse became rapidly weaker and the patient cyanotic and the following day died. Patient was extremely obese. No circulatory features.
1768	14	M.	W.	9 days	Toxemia.	Patient had previously been in the hospital with malaria and Addison's disease. Was taken abruptly ill 2 days before admission with fever. Was deeply intoxicated on admission and grew gradually worse and died on 6th hospital day. No circulatory features.
1654	26	M.	W.	14 days	Toxemia.	Onset of illness 10 days before admission with fever, headache and weakness. Had been delirious before admission. Was extremely ill when he entered hospital; high fever and delirium. Became more and more deeply intoxicated and developed a marked tremor. Died on 4th hospital day. On admission pulse was very irregular and remained so in intervals. Heart sounds clear but approaching embryocardia.
1642	22	F.	B.	Apparently 18 days.	Toxemia. Death preceded by bloody vomiting.	Admitted to gynecologic service complaining of abdominal pain. Operated on and tubes removed; 22 days later second operation for release of intestinal adhesion. Thirteen days after second operation temperature began to rise; 13 days later patient began to vomit blood and continued for 4 days when she died from exhaustion. Throughout course had considerable abdominal pain. No unusual circulatory symptoms.



Anatomical Diagnosis.	Description of Heart	
Gross.	Microscopical.	
Typhoid fever. Hyperplasia of lymph-nodes of intestine with ulceration of Peyer's patches in the ileum and perforation. General fibrinopurulent peritonitis. Acute splenic tumor. Hyperplasia of abdominal lymph-glands. Bronchopneumonia and purulent bronchitis.	Weight 220 gm. Not enlarged. Pericardial and endocardial surfaces smooth. Muscle flecked with grayish points and somewhat opaque in appearance.	Nuclei rather large. Some pigmentation. Slight fragmentation. Areas of cells, mostly mononuclear, about blood-vessels. No definite interstitial infiltration.
Typhoid fever. Clean ulcers in lower ileum. Acute splenic tumor. Pyelitis and suppurative nephritis of right kidney. Edema of lungs. Effusion into pleural cavities.	Weight 300 gm. Not enlarged. Muscle fairly firm, deep red in color and homogeneous.	Fibers look granular. Nuclear changes well marked. Some vacuolization of fibers. Sarcoplasmic increase. Striation of fibers indistinct. Rather extensive and diffuse infiltration throughout the bands of connective tissue consisting principally of large and small mononuclear cells. Some polymorphonuclears and many eosinophils. Several areas of hemorrhage into muscle.
Typhoid fever. Ulceration of Peyer's patches in ileum. Swelling of mesenteric lymph-glands. Acute splenic tumor. Parenchymatous degeneration of kidneys, liver and heart. Chronic adhesive pleuritis. Edema of lungs.	Weight 250 gm. Organ flabby, soft and somewhat blood-stained. Epi- and endocardium smooth. Left ventricle has a grayish opaque appearance and collapses over one's fingers. On tangential section this grayish opacity is more deeply marked.	Fiber changes marked. Fibers appear granular and in some the striation is indistinct. Marked nuclear changes and pigmentation. Some sarcoplasmic increase. Extensive fragmentation. About blood-vessels and radiating into connective tissue bands of cellular accumulation consisting principally of small and large mononuclears. The infiltration restricted almost entirely to the papillary muscles. Several areas of chronic fibroid change. In one area there seems to be some formation of new connective tissue.
Typhoid fever. General peritonitis. Perforation of gall-bladder. Hyperplasia and ulceration of Peyer's patches of lower part of ileum. Hyperplasia of mesenteric lymph-glands. Acute splenic tumor. Parenchymatous degeneration of liver and kidneys. Cholelithiasis. Cystitis.	Epicardium and endocardium smooth. Muscle firm. On section reddish-brown in color and homogeneous throughout. Here and there small gray points can be seen. Coronary arteries normal and free from atheroma.	Nuclear changes and pigmentation unusually well marked. Slight fragmentation. No marked sarcoplasmic increase. Some areas of chronic fibroid change. Some vessels show chronic thickening. Throughout the connective tissue strands the cells are more numerous than normal and some local accumulations about blood-vessels. No localized or marked infiltration.
Typhoid fever. Hyperplasia and ulceration of Peyer's patches and solitary follicles of ileum. Hyperplasia of mesenteric lymph-glands. Acute splenic tumor. Parenchymatous degeneration of liver and kidneys. Obesity. Parenchymatous degeneration of heart muscle.	Weight 420 gm. Organ of large size. Epicardium contains abundant fat. Muscle firm in consistency, reddish-brown in color. Somewhat cloudy. Fresh plaques of sclerosis in coronaries.	Fibers appear granular. Marked nuclear changes and unusually well marked sarcoplasmic increase. No fragmentation. Some diffuse cellular accumulation in interstitial bands but no marked or circumscribed infiltration.
Addison's disease. Congenital atrophy of adrenals. Typhoid fever. Tuberculosis of bronchial lymph-glands.	Weight 170 gm. Surface smooth. Under epicardium of left ventricle several ecchymoses. Muscle firm in consistency. Compact in texture and of a brownish-red color.	The nuclear changes are well marked and considerable pigmentation. No fragmentation. Moderate sarcoplasmic increase. Fibers a little granular. No interstitial lesions.
Typhoid fever. Hyperplasia of lymphatic tissue in intestine with sloughing in ileum and upper colon. Deep ulceration in lower ileum. Acute splenic tumor. Hyperplasia of mesenteric and portal lymphatics. Cloudy swelling of liver and kidneys.	Not enlarged and muscle of rather grayish appearance. Distinctly softer than normal.	Nuclear changes well marked. Considerable sarcoplasmic increase. Some of the fibers appear granular and in some striation is a little indistinct. No fragmentation. Interstitial infiltration very well marked. Starting principally about the blood-vessels the cells radiate along the connective tissue bands. Several infiltrating areas under endocardium. Cells are mostly large mononuclear cells with homogeneous protoplasm and eccentric nuclei resembling plasma cells. There is some interstitial edema. The vessel-walls show some chronic fibroid thickening.
Typhoid fever. Hyperplasia and necrosis of Peyer's patches of ileum. Hyperplasia of solitary follicles of ileum, cecum and ascending colon. Swelling of mesenteric lymph-glands. Acute splenic tumor. Fatty degeneration of liver. Acute nephritis. Chronic pulmonary tuberculosis at right apex. Recent and healed laparotomy wounds. Localized fibrinous peritonitis.	Surface smooth. Muscle firm, brownish-red in color. Below epicardium numerous minute ecchymoses.	Fibers in places appear granular and striation is a little obscured. Nuclear changes are marked. There is moderate pigmentation. Some sarcoplasmic increase. Only slight fragmentation. All the blood-vessels are unusually full of leukocytes and throughout the section the interspaces are peppered with cells, mostly large mononuclears. There is no intense local infiltration. Rather marked interstitial edema about the muscle cells.

TABLE OF CASES OF TYPHOID SHOWING CONDITION OF HEART MUSCLE

Pathological No.	Age.	Sex.	Color.	Duration of Illness.	Cause of Death.	Main Clinical Features.
1618	27	M.	W.	3 weeks.....	Intestinal hemorrhage.	Patient taken ill 3 weeks before admission with fever and chills. During this time had wandered about streets sleeping in markets. Had a large hemorrhage on morning of admission. Was very ill when he entered hospital and evidently suffering from loss of blood. After admission bled continuously from the bowel and died the following day. No special circulatory symptoms.
1630	21	M.	B.	16 days.	Toxemia.	After an illness of 7 days with fever, headache, nausea and some vomiting entered hospital. Was very dull and ill on admission but in good general condition. On 4th day developed pain and tenderness in right iliac fossa which increased in intensity and on the 7th day laparotomy was performed. No intestinal perforation was found; an acute appendicitis with some fluid about the cecum. Patient did well after operation until the 2nd day, when his pulse rapidly rose to 160 and he gradually sank. On admission and after first sound at apex was noted to have a murmurish quality. No other unusual circulatory symptoms noted.
1587	10	F.	W.	25 days.	Hemorrhage. Hemorrhagic typhoid without intestinal lesions.	Entered hospital after being ill 5 days with headache and fever. Patient was deeply intoxicated and on 5th and 6th days had vomiting. On 12th day nose-bleed began. Bleeding from nose and mucous membranes of mouth continued uninterruptedly and patient had blood in stool and hemorrhagic spots in skin. Became extremely anemic and died on 20th hospital day. A very rapid weak pulse the only circulatory symptom. On admission there was a systolic murmur at the apex.
1576	19	M.	W.	29 days.....	Toxemia (?). Died after convulsions.	Patient entered hospital after an illness of 1 week with headache, fever and abdominal pain. Symptoms of toxemia increased in severity. Great muscular twitching developed and after several convulsions patient died on 22nd hospital day. Throughout illness had considerable abdominal pain and tenderness suggesting perforation. Pulse rapid and of small volume. Heart sounds blurred and rhythm, approached embryocardia.
1575	26	M.	.....	26 days?.....	Peritonitis following intestinal perforation.	Entered hospital complaining of epigastric pain. Had been ill 12 days with fever and abdominal pain. The abdominal symptoms became more marked and patient was operated on on the 7th day. After operation grew gradually weaker and died on the 14th day. Pulse rather slow. No other circulatory symptoms.
1152	46	M.	W.	65 days?.....	Exhaustion. Death occurred suddenly.	A prolonged attack of fever with intercurrent relapse. Patient had been ill 6 weeks before admission with fever, pain in chest and cough, although he remained at work. On admission was thin and worn. On 17th day developed left-sided hemiplegia followed by stupor and Cheyne-Stokes breathing. On 23rd day died very suddenly. Circulatory symptoms extremely prominent. On admission signs of mitral insufficiency (systolic murmur and accentuation of pulmonary second sound) and a slow and very irregular pulse. Pulse remained irregular throughout illness. Before death gallop rhythm.
1150	.....	.....	.....	.....	.....	History lost.

# ILLUSTRATING ARTICLE BY LOUIS HAMMAN

## Anatomical Diagnosis.

## Description of Heart

### Gross.

### Microscopical.

<p><b>Typhoid fever.</b> Many dirty-looking ulcers in the lower ileum and cecum. Great swelling of Peyer's patches and solitary follicles. Hemorrhage from bowel. Cloudy swelling of mesenteric lymph-glands, heart muscles and kidneys. Fatty liver. Acute splenic tumor. Fresh bronchopneumonia. Fatty change in endothelium of aorta.</p>	<p>Weight 240 gm. Muscle soft and opaque. Gray in color.</p>	<p>The myocardial changes are extensive. Fibers are granular and in places the striation is obscured. Marked sarcoplasmic increase, some fibers on cross-section having fibril bundles only about the periphery. In some areas the muscle-cells have been completely destroyed. Nuclear changes are marked. Extensive diffuse and intense local areas of infiltration. Large areas of infiltrating cells under the pericardium. Edema of interstitial tissue. Fresh (?) connective tissue formation. Several old areas of connective tissue with fresh infiltration about them.</p>
<p><b>Typhoid fever.</b> Ulcers in ileum and colon. Hyperplasia of mesenteric lymph-glands. Acute splenic tumor. Parenchymatous degeneration of kidneys.</p>	<p>Weight 300 gm. Myocardium flabby, opaque, of a pale yellowish color.</p>	<p>Marked fiber changes. Nuclear changes extensive. Considerable sarcoplasmic increase. Marked fragmentation. Some vacuolar degeneration and in places a few fibers are completely degenerated. The interstitial lesions are definite but not nearly so intense as in other cases. The cells are mostly small and large round cells with eccentric nuclei. Hemorrhage into muscle. Some chronic thickening of arterial walls.</p>
<p><b>Typhoid fever without intestinal lesions.</b> Hyperplasia of lymph-glands. Acute splenic tumor. Anemia, subcutaneous and subserous ecchymoses.</p>	<p>Weight 120 gm. Numerous ecchymoses on epicardium. Muscle pale brown in color. On section are seen a few ecchymoses in muscle substance. Muscle is firm. Numerous ecchymoses on endocardium.</p>	<p>Most extensive fiber and interstitial lesions. Marked sarcoplasmic increase. Many fibers show marked vacuolization. Nuclear changes marked. No special fragmentation. Many muscle fibers have undergone complete disintegration leaving degenerated nuclei. The interstitial changes are extensive and intense. Areas of infiltration under pericardium and throughout the muscle. A striking feature is the large number of eosinophils. Marked hemorrhage into muscle and edema.</p>
<p><b>Typhoid fever.</b> Numerous superficial ulcerations in lower part of ileum, in cecum and in rectum. Older ulceration in the cecum. Enlarged mesenteric glands. Acute splenic tumor. Fatty degeneration of liver and of intima of aorta. Cloudy swelling of myocardium and of kidneys. Fresh bronchopneumonia.</p>	<p>Weight 225 gm. Pericardium normal. Muscle of opaque, reddish-brown color. Somewhat soft.</p>	<p>Nuclear changes moderately well marked. Fibers look granular. In papillary muscle considerable sarcoplasmic increase but none elsewhere. "Cement lines" prominent. No definite fragmentation. Numerous areas of cells under epicardium but no large areas of infiltration. Connective tissue spaces rich in cells but no large accumulations.</p>
<p><b>Typhoid fever.</b> Swelling and ulceration of Peyer's patches and solitary follicles. Perforation of typhoid ulcer. Fibrinopurulent peritonitis. Acute splenic tumor. Hyperplasia of mesenteric lymph-glands. Ulcers of stomach. Acute nephritis.</p>	<p>Weight 270 gm. Muscle quite firm in texture. Brown in color.</p>	<p>Nuclear changes well marked. "Cement lines" apparent and occasional fragmentation. No interstitial change.</p>
<p><b>Typhoid fever.</b> Healed ulcers in intestines. Moderate splenic tumor. Thrombosis of left iliac and femoral veins. Embolism of vena cava inferior. Parietal thrombi in left ventricle. Embolism of smaller pulmonary arteries. Infarction of right lung. Bronchopneumonia. Anemic infarcts of kidneys. Fibrinous pleuritis. Infarction of spleen. Tuberculosis of cervical lymph-glands.</p>	<p>Weight 620 gm. Valves normal except mitral shows slight thickening. Right auricle and ventricle greatly dilated and marked thickening of right ventricle. Left auricle and ventricle somewhat dilated and papillary muscles flattened. Several firm thrombus masses between trabeculae. Muscle soft and flabby. On tangential section shows mottling.</p>	<p>Marked nuclear changes. Pigmentation. Slight fragmentation. Fibers show sarcoplasmic increase and some vacuolization. In small areas the fibers seem to be undergoing complete degeneration. Numerous areas of interstitial infiltration some beginning under epicardium others in the connective tissue bands. Cells small and large mononuclears with some polymorphonuclears and large cells with eccentric nuclei. Areas of chronic fibroid change with fresh infiltration.</p>
<p><b>Typhoid fever.</b> Ulceration of Peyer's patches and solitary nodules in ileum and colon. Acute splenic tumor. Parenchymatous degeneration of kidneys and liver. Ulcers in larynx. Pulmonary infarct and edema. Hyperplasia of esophageal lymph-glands. Gastric and intestinal hemorrhages. Hemorrhagic diathesis.</p>	<p>Heart muscle pale, feels soft.</p>	<p>Moderate nuclear changes and pigmentation. Some fragmentation. Fibers look granular. No interstitial changes.</p>

TABLE OF CASES OF TYPHOID SHOWING CONDITION OF HEART MUSCLE

No.	Age.	Sex.	Color.	Duration of Illness.	Cause of Death.	Main Clinical Features.
39	20	F.	B.	28 days.....	Acute lobar pneumonia.	Ill for 18 days with fever, headache and abdominal pain before admission to hospital. On day of admission and subsequent 3 days blood in stools amounting in all to about 1 liter. On 3rd day patient developed lobar pneumonia and general condition became progressively worse to time of death on 14th day. Heart sounds feeble and pulse occasionally irregular. Later first sound reduplicated at apex.
37	17	M.	B.	25 days.....	Toxemia. Died rather suddenly.	Ill for 16 days before admission with fever and feeling weak and miserable. Patient had a very high temperature and later became deeply intoxicated. On 2nd day after admission, embryocardia; pulse very rapid and at times irregular.
32	21	M.	W.	16 days.....	Peritonitis following intestinal perforation.	Onset 12 days before admission with headache, general malaise and fever. On 4th day patient developed an abscess in left submaxillary gland which was incised. On 17th day had small hemorrhage followed by symptoms of perforation and general peritonitis. Sank rapidly and died on 24th day. Systolic murmur at apex with marked accentuation of both second sounds.
15	25	M.	B.	16 days.....	Peritonitis following intestinal perforation.	Patient entered hospital in good general condition after having been ill 2 weeks with fever, weakness and nausea. On 3rd day symptoms of perforation and operation the same day; 2 days later a second operation for general peritonitis followed in 10 hours by death. Soft systolic murmur at apex with accentuation of second pulmonary sound.
20	40	M.	W.	13 weeks! History of onset is indefinite.	Toxemia.	Patient ill for 10 weeks before admission with stomach trouble and chills and fever. Condition fairly good but mind wandering. Patient has an extensive pleurisy on left side; phlebitis of right popliteal vein. After admission had a number of chills followed by profuse sweating. Jaundiced on admission and remained so to time of death. Toward end breathing became labored and patient cyanotic. Pulse gradually failed. Last few days of life pulse was irregular. Second pulmonary sound accentuated. No murmurs.
75	28	M.	W.	24 days.....	Toxemia.	Onset 10 days before admission with fever, headache and diarrhea. In good condition on admission but later became deeply intoxicated with marked subsultus and rigidity of arms and legs. Severe nosebleed on 13th day followed by blood in stools. On admission heart sounds clear but later a systolic murmur developed with accentuation of the second pulmonary sound. Toward end pulse became small and thready and very irregular. Patient was deeply cyanosed and developed Cheyne-Stokes breathing.
47	31	M.	B.	27 days.....	Peritonitis following intestinal perforation.	Entered hospital in good general condition after an illness of 12 days with fever and headache. On 5th day had abdominal pain and there were indefinite signs of perforation. On the 13th day the signs became prominent. Operation on 15th day followed by death on the 16th. Heart sounds described as being faint and distant and the first sound at apex as of an indefinite quality.
17	21	M.	B.	23 days.....	General staphylococcus infection	Onset of illness 9 days before admission with headache and pain in limbs and weakness. Patient in good general condition on admission but later became irrational and drowsy and dull. On 9th day there was pain and marked swelling of right parotid gland which was opened and drained on the 11th. Patient grew gradually worse and died on the 13th day. No circulatory symptoms other than the first sound having a murmurish quality.

ILLUSTRATING ARTICLE BY LOUIS HAMMAN

Anatomical Diagnosis.	Description of Heart	
	Gross.	Microscopical.
Typhoid fever. Hyperplasia, ulceration and necrosis of Peyer's patches and solitary follicles. Acute enlargement and necrosis of mesenteric glands. Acute croupous pneumonia. Pulmonary edema. Cloudy swelling of liver and kidneys. Acute splenic tumor. Chronic adhesive peritonitis. Chronic adhesive pleuritis. Acute fibrinous pleurisy.	Weight 200 gm. Muscle pale and almost pure brown in color.	Fibers in places are granular. Marked nuclear changes. Moderate sarcoplasmic increase. Extensive fragmentation. Small accumulations of cells under epicardium and about blood-vessels. No infiltration. Hemorrhage into muscle.
Typhoid fever. Ulceration in colon and lymphatic hyperplasia. Ulceration in ileum. Hyperplasia of mesenteric lymph-glands. Acute splenic tumor. Cloudy swelling of liver and kidneys. Slight bronchopneumonia and atelectasis. Old pleural adhesions.	Weight 395 gm. Few small ecchymoses on posterior surface.	Nuclear changes marked. Pigmentation moderate. "Cement lines" prominent but no fragmentation. Sections not very satisfactory.
Typhoid fever. Ulcers in the ileum. Perforation of an ulcer. Generalized peritonitis. Acute splenic tumor. Hyperplasia of mesenteric lymph-glands. Suppurative inflammation of left submaxillary gland. Broncho-pneumonia with abscess formation.	Valves are delicate and compensate. Muscle appears slightly softened and is rather opaque and cloudy in appearance.	Fibers look granular. Nuclear changes and pigmentation marked. Marked sarcoplasmic increase. No fragmentation. Areas of infiltration under epicardium and rather extensive infiltration in papillary muscle. Artery walls somewhat thickened and there are areas of apparently chronic fibroid change with fresh infiltration about them.
Typhoid fever. Ulceration of ileum and perforation of intestinal wall. Acute general fibrinopurulent peritonitis. Acute splenic tumor. Hyperplasia of lymphatic glands. Cloudy swelling of liver and kidneys.	Weight 250 gm. Pericardium slightly congested. Valve margins clear.	Fibers a little granular. Nuclear changes very well marked and moderate pigmentation. No sarcoplasmic increase. No vacuolization. Slight fragmentation. No interstitial changes.
Typhoid fever (healing ulcers). Acute splenic tumor with infarctions. Chronic aortic endocarditis. Chronic diffuse nephritis. Slight bronchopneumonia. Adhesions between diaphragm and left lung and spleen.	Pericardium smooth and glistening. Aortic valves somewhat thickened. Two coronary segments bound together. Muscle very soft and flabby.	Fibers are granular. Marked nuclear changes and extensive fragmentation. Considerable sarcoplasmic increase. Capillaries unusually full of leukocytes but not interstitial infiltration.
Typhoid fever. Medullary swelling of lymphatic tissue in intestine. Slight ulceration and swelling of mesenteric lymph-glands. Acute splenic tumor. Hemorrhage into intestinal canal. Chronic adhesive pericarditis. Chronic pleuritis.	Pericardium adherent over whole heart by veil-like adhesions. Heart weight 310 gm. All valves delicate and competent. Endocardium smooth. Myocardium apparently normal.	Fibers in places granular and striation obscured. Nuclear changes marked. "Cement lines" evident but no separation. Some sarcoplasmic increase but this feature not marked. Several areas of rather extensive infiltration, especially in papillary muscle. Many large areas of infiltration under the epicardium. Many of the characteristic cells found in all the cases with infiltration but especially predominating in Case 27.
Typhoid fever. Intestinal perforation. General fibrinopurulent peritonitis. Healing ulcers in ileum, cecum and appendix. Slight ileocolitis. Suppurating peritoneal glands. Acute splenic tumor. Cloudy swelling of kidneys.	Weight 250 gm. Muscle a little opaque; firm; apparently but little altered from normal.	No marked changes other than the nuclear, which are large and swollen and distorted. Some segmentation. Areas of small round cells under the pericardium and throughout the connective tissue spaces but no definite infiltration between muscle fibers.
Typhoid fever. Swelling and superficial ulceration of follicles of small and large intestines. Diffuse hemorrhagic infiltration of mucous membrane of intestines. Distention of gall-bladder with pericystic inflammation. Liver abscess and necrosis. Abscess of gastrohepatic lymph-glands. Multiple lung abscesses. Bronchopneumonia. Acute fibrinous pleurisy. Multiple kidney abscesses. Acute splenic tumor. Parenchymatous degeneration of kidneys. Suppuration of parotid glands.	Weight 320 gm. Pericardium and epicardium smooth. Valves delicate. Consistency of heart's flesh firm.	Fibers are granular and in some striation obscured. Nuclear changes marked. "Cement lines" prominent but no fragmentation. Only moderate sarcoplasmic increase. Numerous areas of infiltration under the epicardium and endocardium. Infiltration of muscle particularly marked in papillary muscle.

## THE FUNCTIONAL DISTURBANCES IN PAROXYSMAL TACHYCARDIA

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In studying the attacks of tachycardia which have been known since the description of Cotton in 1867, and which Bouveret has designated as "essential" or "idiopathic" paroxysmal tachycardia, it is necessary to distinguish very carefully between "paroxysms of tachycardia" and idiopathic paroxysmal tachycardia. In the ordinary tachycardias of emotion, excitement or exercise, the pulse-rate gradually quickens and finally reaches its maximum, and when the cause is over, the rate subsides gradually. In the idiopathic paroxysmal tachycardia the rate rises and falls suddenly. The heart-beats just preceding the paroxysm have the usual rate. With the second beat of the paroxysm the heart-beat is already about double that of the preceding and has reached the maximal rate of the paroxysm. The rate then continues practically unchanged throughout the paroxysm, and without warning, the paroxysm subsides as suddenly as it has come.

This sudden onset and sudden subsidence is quite unique and distinct from the ordinary effects of the cardiac nerves. The changes of rate from stimulation of the cardiac nerves, from emotion, excitement or exercise never are so sudden. Their mode of action is typified by a patient who, during a year after an attack of typhoid fever, was subject to attacks of palpitation and rather sudden onsets of tachycardia, so that there was a suspicion of idiopathic paroxysmal tachycardia. At the beginning of the examination his pulse was 60 per minute. As I began to get the cardiosphygmograph ready, he became excited, and in successive quarters of a minute his pulse-rate rose from 15 to 20 to 25, and in the last quarter of a minute to 30. Within one minute the pulse-rate had doubled, but the change of rate was gradual and not sudden. It was evident that this was not idiopathic paroxysmal tachycardia, and the subsequent history of the patient proved conclusively that it was not.

The views of the older writers, that paroxysmal tachycardia is the result of a vagus neurosis, seem to be disproved. Gerhardt and later Hirschfelder have shown that paroxysms cannot be produced in patients by paralyzing the vagi with atropin between attacks; and even stimulating the accelerator nerves by exercise, while the patient's vagi are

paralyzed with atropin, fails to bring on an attack. Moreover, S. Hyman, working under Sir Victor Horsley, has produced lesions of the vagus nuclei in the medulla in a large series of dogs and monkeys, but this has never given rise to paroxysmal tachycardia. It is evident, therefore, that another mechanism must be sought.

The venous tracings taken from patients with paroxysmal tachycardia have shown two types, and a number of cases of each have been reported: (1) the auricular type, in which the auricular presystolic (*a*) wave is preserved throughout the attack, and (2), the ventricular type, in which the *a* wave is absent from the venous pulse.

It would appear from clinical manifestations and experimental evidence that these two types represent merely different grades in the intensity of the same condition and not the result of totally different causes.

The cause of this change probably lies not in the extracardiac nerves, but in an increased irritability of the heart-muscle, or, if the neurogenic theory is adopted, in the nerve-endings within the heart-muscle. Although such changes in rate have never been observed from stimulation of nerves, they have been produced by increasing the irritability and rhythmicity of the muscle. Ludwig and Hoffa in 1849 and, since then, numerous other observers have demonstrated that weak faradization of the mammalian heart gave rise to a sudden increase in the heart-rate, while strong stimulation caused fibrillation. Hirschfelder has shown that this increase in rate amounts to an almost exact doubling, and that it comes on absolutely suddenly, just as is found in paroxysmal tachycardia. It also subsides suddenly, within the space of a single beat, which still further bears out the parallelism (Fig. 3A and B).

The exact effect of such faradization varies with the intensity of the stimulus and with the irritability of the heart. If the stimulus is a very weak one, there is no doubling of the rate, but there are occasional extrasystoles. The extrasystoles may even accompany every alternate beat and give rise to a continuous bigeminal pulse.

If the stimulus is increased very slightly, the first effect observed is a sudden approximate doubling of the rate of the auricles (Fig. 1). The ventricles follow each auricular beat, but the conduction time during the paroxysm is definitely longer than at the normal rate; that is, the conductivity is diminished during the paroxysm (Fig. 2).

Most of these paroxysms, however, last only as long as the faradization itself, and the heart rate returns to normal, as soon as the stimulation is stopped.

If the faradization is repeated several times in rapid succession, or if the intensity of the stimulus is increased, or on the other hand, if the irritability of the heart is of high grade, the auricles and ventricles may contract absolutely synchronously (Fig. 3).

Since it is difficult to conceive that conduction from auricle to ventricle would be so rapid as to occupy an almost infinitesimal time, it may be assumed with Hering and Mackenzie, that in this case the car-

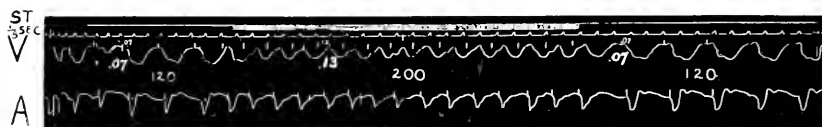


Fig. 1.—Mild faradization of the auricle. Tachycardia, with slowed conduction, lasting as long as the stimulation. Downstrokes = Systole; time in 1/5 seconds: A = auricular contractions; V = ventricular contractions; St = stimulation of auricle.

diac impulse arises in the Purkinje fibers of the auriculoventricular bundle and is conducted simultaneously in both directions, a condition which Mackenzie terms a "nodal rhythm."

Rhythms of this type have been demonstrated by Matthews and by Cushny after aconite poisoning, but it is not possible to prove absolutely that in the mammal they originate in the cells of the auriculoventricular bundle. Dr. G. S. Bond, in my laboratory, has recently bridged this gap by studying the effects of aconite poisoning in the frog's heart. He



Fig. 2.—Slightly more intense stimulation. Tachycardia, with quickened conduction, outlasting the period of stimulation. Time in seconds.

has found that in the frog's heart one can watch the ring of muscle at the auriculoventricular junction contract. Normally it contracts just after the auricle and just before the ventricle, but in aconite poisoning one occasionally encounters extrasystoles in which the auriculoventricular ring contracts first, and this is followed by the systole of the auricles and ventricle, which contract at the same instant. The simultaneous



contractions of auricle and ventricle in the mammal seem exactly similar to this, and hence are assumed to be auriculoventricular in origin.

If the faradic stimulus is still more intense, the auricles pass at once into fibrillary contractions, and the ventricles respond with a sudden doubling of the rate, sometimes regular and sometimes irregular, which is almost exactly the same rate as that which occurs when the auricles are undergoing coordinate contractions at the doubled rate (Fig. 4).

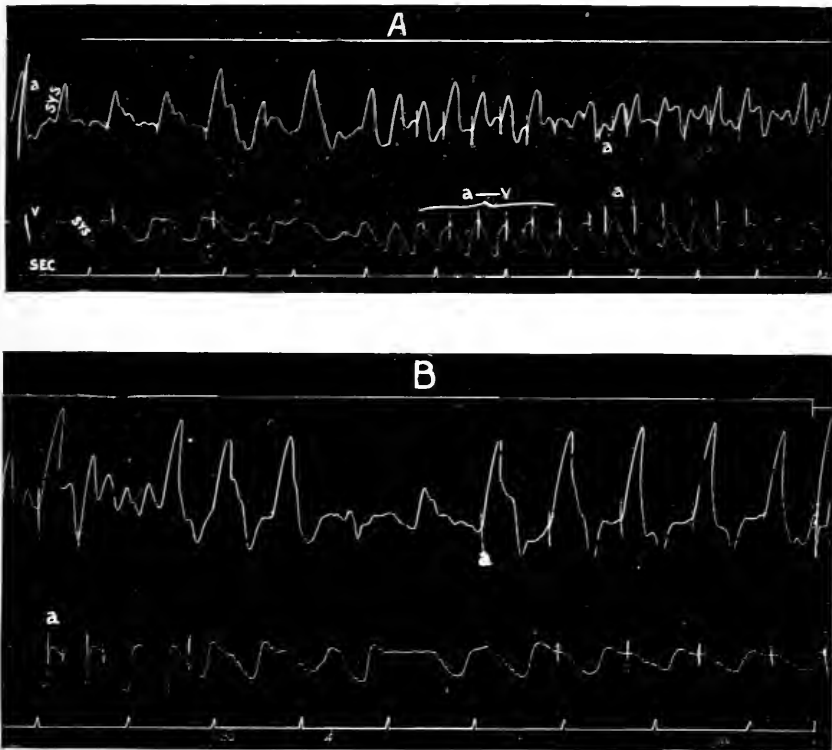


Fig. 3.—Effect of more intense stimulation: A, onset of paroxysm; B, subsidence of paroxysm. Tracing of auricular contractions made by the suspension method (upstrokes=systole); that of ventricles by tambour transmission (downstrokes=systole). A short series of simultaneous contractions of auricles and ventricles (auriculoventricular rhythm, a-v) is terminated by an auricular extra-systole (a), after which the auricle initiates the rhythm. Auricles (a): upstrokes=systole. Ventricles (v): downstrokes=systole.

The electrocardiogram shows that the fibrillating auricles give rise to very numerous stimuli at an irregular rate of from 300 to 900 per minute, too fast for the ventricles to follow; but the intensity of each electrical variation is of almost the same magnitude and is sometimes even

greater than that of a normal impulse. MacWilliam and later Hirschfelder have shown that, when stimuli are thrown into the heart too fast for it to follow, it frequently responds by a doubling of the rate rather than by a contraction in response to each individual stimulus, and the rapidly recurring stimuli from the fibrillating auricles present exactly these conditions. The auricular fibrillation and the ventricular tachycardia cease abruptly sometimes spontaneously, sometimes after stimula-

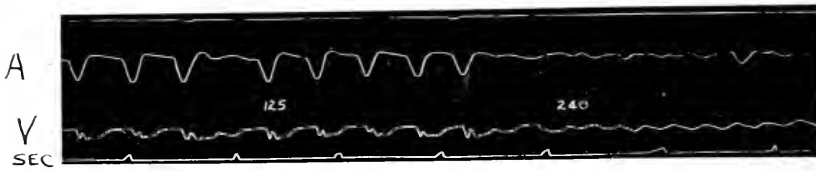


Fig. 4.—Still more intense stimulation. Fibrillation of the auricle sets in, and is accompanied by tachycardia of the ventricle. Downstrokes == systole.

tion of the vagi (Fig. 5). Sometimes the tachycardia resists the vagus stimulation and persists in spite of it (Fig. 6).

Besides these conditions fibrillation of the auricles with the accompanying tachycardias have been produced experimentally in several ways.

Garrey and Hewlett produced it after the cessation of vagus stimulation, but only when the heart had already been in a state of greatly increased irritability. Cushman and Edmunds, who were the first to associate it with paroxysms of arrhythmias, though not with paroxysmal tachycardia, obtained fibrillation in many animals poisoned with morphin. Thomas Lewis has recently produced such attacks of auricular fibrillation and

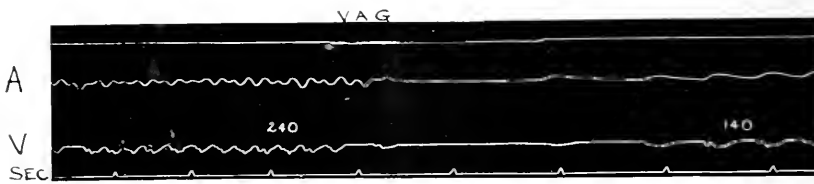


Fig. 5.—Effect of stimulation of the vagus (vag) on a mild paroxysm, bringing about cessation of the tachycardia.

ventricular tachycardia in dogs, about an hour after ligature of the right coronary artery, thus simulating the association of coronary sclerosis and paroxysmal tachycardia to which Romberg has called attention. The fact that paroxysmal tachycardia is a disease common in otherwise healthy children and in the young, and that it often lasts from thirty to fifty

years would indicate that coronary sclerosis is not the usual etiologic factor.

In this series of experiments Lewis has reproduced experimentally all the forms of auricular, auriculoventricular and ventricular tachycardias which one can obtain by faradic stimulation, and has furnished further evidence for the belief that they are all to be regarded as transitional forms of the same general disturbance.



Fig. 6.—Effect of stimulation of the vagus upon a severe paroxysm, causing temporary stoppage. The tachycardia is then resumed.

Moreover, Cushny has recently produced all these forms of cardiac action in aconite poisoning.

The question is, therefore, how the experimental findings explain the clinical. It is quite evident that in suddenness of onset and cessation, in the form of venous pulse, in the partial independence of vagus control, the experimental paroxysms resemble the clinical. The resemblance could be absolutely clinched by means of the electrocardiogram.

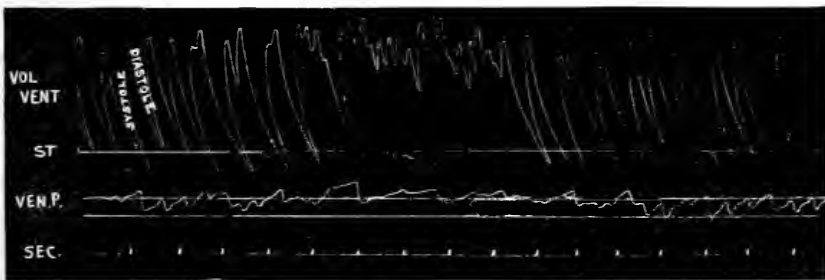


Fig. 7.—Diminution in the volume of the ventricles and rise of venous pressure in experimental paroxysmal tachycardia. Vent. Vol.=volume of the ventricles; Ven. P.=venous pressure; St.=stimulation of the auricles with induction shocks.

Thus far a few satisfactory electrocardiograms have been made by Thomas Lewis, but only in cases of the first type with auricular contractions well marked on the venous pulse. In these he has found, of course, well-marked auricular (P) waves on the electrocardiogram, and

consequently has concluded that auricular fibrillation is not a factor in paroxysmal tachycardia. Apparently he has entirely overlooked the cases of the second type, with the ventricular venous pulse. These are often the severest cases, and, in them, from analogy with his other cases of ventricular venous pulse, as well as from the experimental results, one would expect to find evidences of auricular fibrillation.

Most of the symptoms of paroxysmal tachycardia seem to be referable to the disturbances in the distribution of the blood within the vessels. As will be seen in the tracing (Fig. 1) very much less blood enters the heart in the short diastoles, and consequently the blood stagnates in the veins and the venous pressure rises. Occasionally, in man it rises to 26 cm. of water, as recorded by Hooker and Eyster, about as high as in broken compensation, so that the veins of the neck become distended and pulsate, and the liver swells, and even edema may set in.

When the attack subsides there is a sudden inrush of blood into the heart, which distends the heart and gives rise to the anginal symptoms that are so common at the termination of the attack.

As will be noticed, so little blood enters the ventricles during the attack that very little can be put out at each systole, and consequently the blood-pressure falls and the patient suffers from weakness, giddiness, and *muscae volitantes*, and occasionally even fainting spells, all the result of depletion of the arteries and of cerebral anemia.

Dietlen and other observers with the *x*-ray found that the hearts of patients often became smaller during the attacks. In the volume curves taken in the experimental paroxysms will be noticed that the same thing has taken place. The underfilling of the heart causes its total volume to diminish very much. It is seen, therefore, that, in both the clinical condition and its experimental simulation, there is the absolutely abrupt onset and abrupt cessation of an intense tachycardia, associated with a great increase in the irritability of the heart, during which the cardiac impulse may originate in any of several different ways; that the milder attacks of this tachycardia may sometimes be stopped by influences which stimulate the vagi, but the severer ones cannot, and hence they cannot be reached by our ordinary therapeutic measures; that the mere tachycardia itself prevents the adequate filling of the heart, thus bringing about symptoms due to venous stasis and symptoms due to cerebral arterial anemia; and that the inrush of blood at the end of the paroxysm gives rise to cardiac dilatation, which causes the feeling of intense constriction at the termination of the attack.

In other words, the picture produced in the laboratory simulates and accounts for the clinical picture, the physical signs, and the symptoms of the patient.

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# AN EXPERIMENTAL STUDY OF THE PHARMACOLOGY OF ERGOT\*

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This research was started as an investigation of the quality of ergot which is at present on the market, and to find a means of improving it. For the purpose of determining the quality of ergot in the light of the knowledge of the chemistry of this subject, the only method which seemed available was the physiological test; but from the beginning, we were impressed with the desirability of establishing if possible, a chemical method for the standardization of this drug. The biological assay of drugs is commercially possible only for large manufacturing houses, since it involves the necessity of employing a separate expert and even under the best conditions, can never be regarded as more than approximately accurate; whereas the proper chemical test should, at least theoretically, be reliable within a very small limit of error. As a result of our studies, we have finally developed a chemical method for the assay of ergot, which in our opinion, is more reliable than any physiological test for this drug which has ever been suggested. For a proper understanding of the basis of the methods we shall suggest and of the evidence of their reliability, it is necessary that we go into the question of the physiological effect of ergot and of the nature of its active principle. Therefore, we shall divide the paper into four sections: "The Physiology of Ergot," "The Chemistry of Ergot," "The Biological Assay" and "The Chemical Assay." In the two introductory sections, it is not our intention to consider in detail the work which has been done on the physiology and chemistry of this drug, but to present chiefly the experimental results of our own investigations.

## THE PHYSIOLOGY OF ERGOT

The use of ergot in medicine may be dated from the paper of Stearns,<sup>1</sup> in which attention was directed to the stimulating influence of the drug upon the uterine muscles. In 1870 Holmes<sup>2</sup> demonstrated that the intra-

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\* A part of the expenses of this research was defrayed by a grant from the American Therapeutic Society.

\* From the Laboratory of Pharmacology, University of Pennsylvania.

2. Holmes: *Arch. de physiol. norm. et path.* 1870, iii.

1. Stearns: *New York Med. Repository*, 1807.

verous injection of the drug gave rise to a marked rise in the blood-pressure, which he attributed to vasomotor constriction. In 1906 Meltzer and Auer found that ergot increased the activity of the intestinal muscles, and in the same year, Dale<sup>3</sup> showed that a similar effect was exercised on practically all the unstriated muscles of the body. There can be

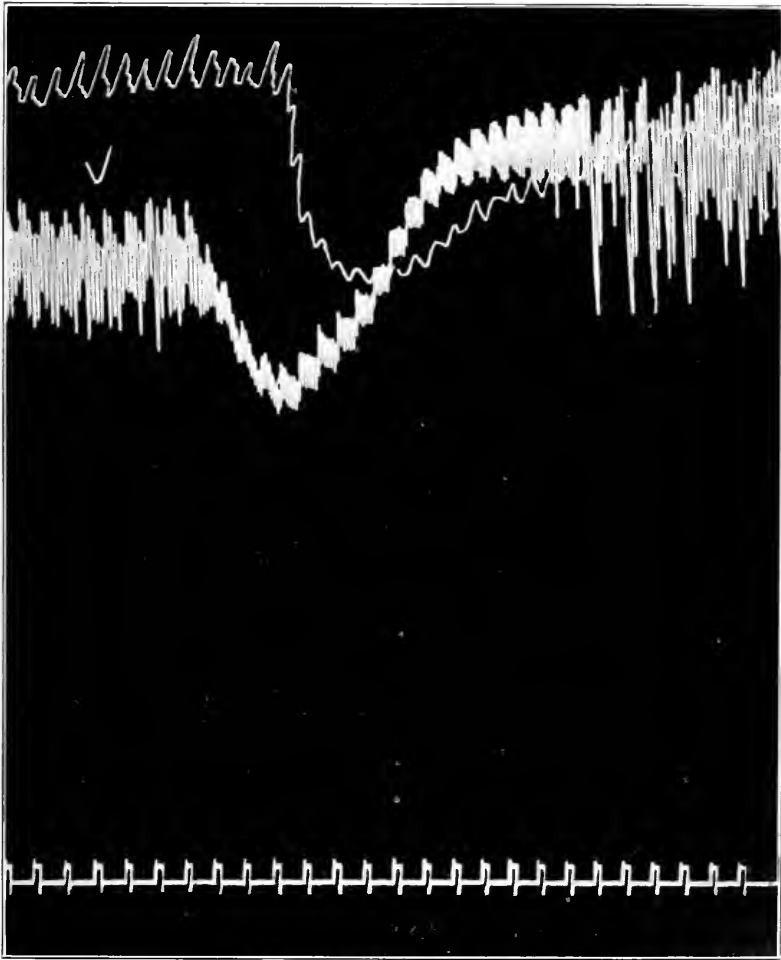


Fig. 1. Showing effect of ergot on blood-pressure and kidney volume. At arrow injection of 0.16 gm. per kilo. Time marker = 5 seconds.

little doubt but that the increased contractions of the uterus and the vasomotor stimulation are part of a wide-spread effect of the drug, involving all involuntary muscle.

3. Dale: *Jour. Physiol.*, 1906, xxxiv, 163.

There has been some difference of opinion as to whether the stimulant influence on the muscle is the result of an action on the nerve centers or a peripheral effect, either on the terminals of the nerve or the muscle itself. Hemmeter<sup>4</sup> was unable to obtain any evidence of a stimulant

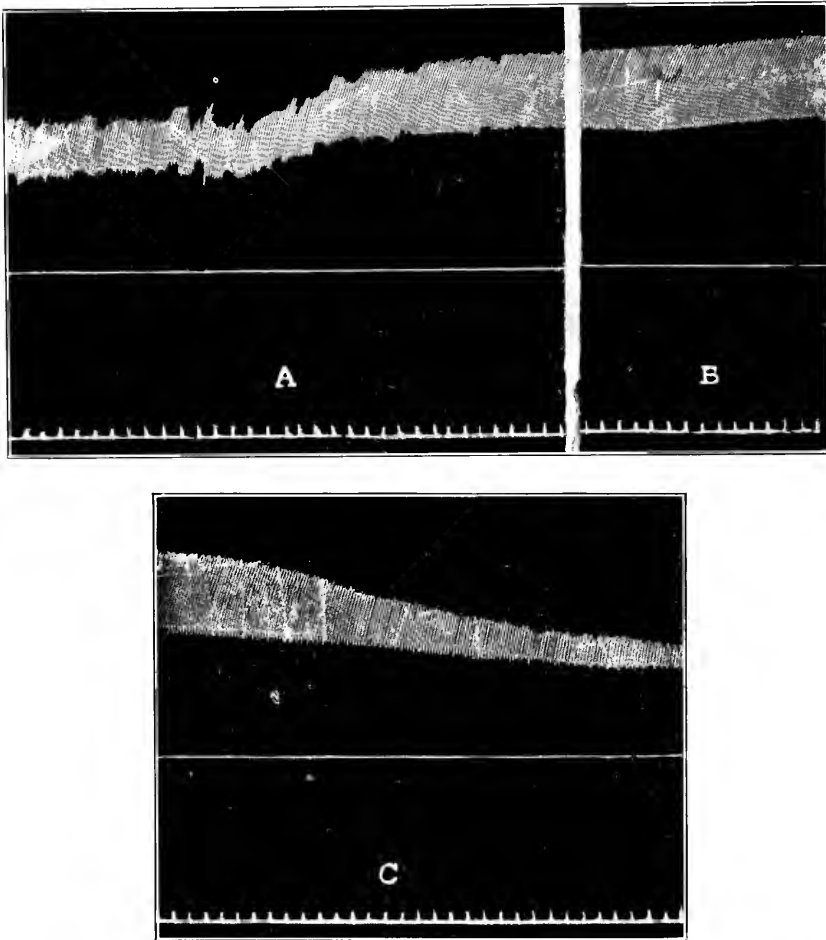


Fig. 2. Showing increase of pulse-pressure caused by ergot. Tracing by Hürthl's manometer. Both vagi have been cut. At V inject 0.16 gm. per kilo. Interval between A and B: 3 minutes (0.32 gm. ergot); between B and C 6 minutes. Time marker = 2 seconds.

influence on either the uterus or the vascular system after destruction of the spinal cord; Wood<sup>5</sup> also reached the conclusion that ergot did not

4. Hemmeter: *Med. News*, Philadelphia, 1891, lxii.

5. Wood: *Philadelphia Med. Times*, 1874, iv, 518.



produce a rise of pressure after destruction of the vasomotor centers. These authors concluded, therefore, that the action of ergot was central. On the other hand, the experiments of Dixon, of Dale and others seem to demonstrate clearly that the destruction of the medulla does not prevent the action of the drug on the circulation, and Kehrer<sup>6</sup> found that isolated strips of uterine muscle were stimulated by ergot.

In our own experiments, we have found that the rise of pressure after destruction of the vasomotor centers was even greater than in the normal animal. For the purpose of excluding central vasomotor effects, we have used two methods which yielded similar results. The first is the common method of cutting the spinal cord in the cervical region, and the second, which we prefer because there is no loss of blood, is that described in a paper by Asher and Wood,<sup>7</sup> of injecting paraffin into the internal carotid artery with sufficient force to block the circle of Willis and the vertebral arteries, so that the vital centers are killed by acute anemia. In Table I are presented the results of two of these experiments.

Most authors have laid considerable stress on the primary fall of blood-pressure which occurs after the intravenous injection of a preparation of ergot, and Holmes attempted to argue from this the occurrence of constriction of the pulmonary vessels.

TABLE I.—RESULTS OF TWO EXPERIMENTS ON EFFECT OF ERGOT ON CIRCULATION, EXCLUDING CENTRAL VASOMOTOR EFFECTS

Time,*	Pressure,	EXPERIMENT 1.—PARAFFINED MEDULLA
0	73	Inject 0.30 gm. per kilo fluidext. ergot Squibb No. 2
2	153	
5	184	
10	167	
25	143	
..	....	Post-mortem showed circle of Willis and both vertebral arteries completely filled with paraffin.
Time.	Pressure,	EXPERIMENT 2.—CUT CORD
0	91	Inject 0.20 per kilo fluidext. ergot Squibb No. 2.
1 <sub>2</sub>	65	
1	140	
3	156	
5	150	
10	150	
20	159	
30	147	Post-mortem showed cord completely severed between first and second cervical vertebrae.
..	....	

\* Throughout this paper the column headed "Time" means minutes since beginning of the experiment, and "Pressure" means millimeters of mercury.

6. Kehrer: Arch. f. exper. Path. u. Pharmacol., 1909, xlix, 266.

7. Asher and Wood: Ztschr. f. Biol., 1899, xix, 307.

In our experiments, the primary fall of blood-pressure has not been a constant phenomenon. We have observed it frequently and almost regularly with doses equivalent to more than 0.3 gm. per kilo. When, however, the dose does not exceed 0.16 the pressure-fall almost never occurs, and after hypodermic administration of the drug, we have not observed it. In our opinion, it cannot be regarded as a part of the physiological action, but is really a poisonous effect from the use of too large doses.

Our plethysmographic studies have shown a contraction of the vessels of the kidney and an enlargement of those of the limb. The latter does not always occur and is probably passive in origin, due to the blood forced out of the more powerful vascular areas by the high pressure.

Recently Dixon has stated that ergot has a stimulant influence on the cardiac muscle as well as upon the arterial muscles. The article in which we saw this statement contains no experimental evidence of its truth and we have been unable to find the data on which the conclusion is based. We are, however, inclined to accept its truth, although our experimental data on the point are not conclusive. After section of the pneumogastric nerve, we find that the pulse-pressure as measured by a Hürthl manometer is very greatly increased by the physiological dose of the drug, and that after toxic doses, the size of the pulse-wave increases and decreases as the blood-pressure ascends and, later, falls. We have attempted to confirm this belief by studies on the isolated heart, but our results so far, have not been definitive.

One other point, which requires mention as bearing on the elaboration of a means of physiological assay, is the duration of the vasomotor constriction. Cronyn and Henderson\* state that the most prolonged rise of blood-pressure they have ever observed following the injection of ergot, lasted but forty minutes; we have, however, in a number of experiments, found the effects to last much longer. The longest we have observed is a little over two hours, but as the experiment was not continued and the pressure was still decidedly above the normal, it is fair to conclude that the effect is an enduring one. Our explanation of the comparatively short duration of the vascular stimulation sometimes encountered is improper dosage. If the dose be too small, it is evident that we cannot expect the full physiological action of the drug, and on the other hand, if the dose is too large, the toxic depressant action becomes manifest and forces the blood-pressure down. In the latter instance, the pressure generally, but not always, falls decidedly below the normal.

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\* Cronyn and Henderson: Jour. Pharmacol. and Exper. Therap., 1909, i, 203.

## ACTIVE PRINCIPLE

It is not our intention to go into the history of the search for the active principle of ergot, as it has been well summed up by a number of previous writers, but only to mention briefly a few points which bear directly on certain new facts which we have to offer on this subject.

In 1875, Tanret<sup>8</sup> described a crystalline alkaloid which he named ergotinin. This was subsequently, however, shown to be physiologically inert. In 1884, Kobert<sup>9</sup> ascribed the activity of ergot to two principles, one of which was a resinous acid which he called sphacelinic acid, and the second an alkaloid to which he gave the name of cornutin. (It may be noted in passing that the cornutin of Keller is an entirely different body, probably a mixture of ergotinin and hydro-ergotinin). More recent investigations, however, have thrown doubt on the natural occurrence of cornutin, and it is probably a decomposition product, which does not occur as such in ergot; and sphacelinic acid is not a pure proximate substance. Jacobi<sup>10</sup> found in ergot a non-nitrogenous body which was neither an acid nor a glucosid, and was highly active physiologically. This body, to which he gave the name of sphacelotoxin, he regarded as the active ingredient of Kobert's sphacelinic acid. He believed that it was found in ergot in the form of two loose combinations, in one with an acid body (chrysotoxin), in the other with an alkaloid (secalintoxin). In 1906 appeared two articles, one by Kraft,<sup>11</sup> the other by Barger and Carr,<sup>12</sup> describing a new alkaloid, to which the latter investigators gave the name of ergotoxin, but which Kraft showed to have the same empirical formula as ergotinin plus one molecule of water, and therefore named hydro-ergotinin. Barger and Dale,<sup>13</sup> in their earlier communications claimed that the activity of all the substances which had been suggested as the active principle of ergot was due to contamination of these substances with ergotoxin which is an extremely powerful stimulant. Recently, however, they have found that para-hydroxyphenylethylamin, a principle which Barger and Walpole had previously separated from putrid meat infusions, occurs in ergot and has a similar action to the hydro-ergotinin. The substance clavin, isolated by Vahlen<sup>14</sup> and claimed by this investigator to be a uterine stimulant, has been shown by Dale and also by Cushny,<sup>15</sup> to be inert.

8. Tanret: *Compt. rend. Soc. biol.*, 1875, lxxxi, 896.

9. Kobert: *Arch. f. exper. Path. u. Pharmacol.*, 1884, xviii, 316.

10. Jacobi: *Arch. f. exper. Path. u. Pharmacol.*, 1897, xxxix, 85.

11. Kraft: *Arch. d. Pharm.*, 1906, cxxlv, 336.

12. Barger and Carr: *Jour. Chem. Soc.*, 1907, xci, 337.

13. Barger and Dale: *Jour. Physiol.*, 1909, xxxviii.

14. Vahlen: *Arch. f. exper. Path. u. Pharmacol.*, 1908, ix, 42.

15. Cushny: *Jour. Physiol.*, 1906, xxxv, 1.

The two substances which seem to us to have the best claims to be regarded as the active principle of ergot are Jacobi's sphacelotoxin and hydro-ergotinin (ergotoxin). Barger and Dale strongly contest the claim of Jacobi that sphacelotoxin is a chemical individual. They assert that the activity of this resinous body is due to contamination with the alkaloid ergotoxin (hydro-ergotinin): although Jacobi claimed to have isolated a small quantity of sphacelotoxin free from nitrogen, and physiologically active, the evidence brought forward to demonstrate the absence of nitrogen is not accepted by the English investigators, and we must

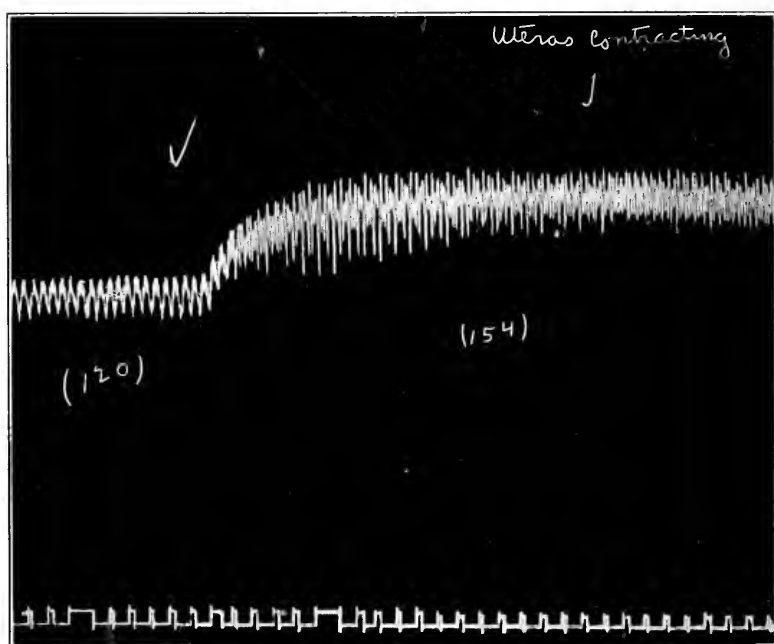


Fig. 3. Showing activity of body extracted by benzol from ergot. At V injection of 0.001 gm. per kilo. Time marker = 5 seconds.

confess that our views agree with those of Barger and Dale. The quantity of nitrogen in sphacelotoxin according to our experiments is approximately 1.3 per cent., and with the extremely small quantities of the principle with which Jacobi was working, it is entirely possible that the nitrogen might have been overlooked.

We have separated from ergot by means of benzol, a body of great potency, a dose of 0.0006 gm. per kilo being sufficient to cause a distinct rise of blood-pressure. On account of the large amount of fatty matter

in crude ergot, we have found it more advantageous first to extract with dilute alcohol, precipitate the resinous matter from this fluidextract with water and then to extract this precipitate with benzole. The body which we have separated by this process is of an amber yellow color, soluble in acetone, ether, ethyl acetate, chloroform, alcohol, benzol, alkalies and strong mineral acids; insoluble in petroleum benzin, water or dilute acids. If its alkaline solution be acidulated, a turbidity is produced, but the precipitate is no longer soluble in benzol, showing that some chemical change has occurred during its union with the alkalies. When boiled in a porcelain dish with sodium hydroxid, a cherry red color appears at the edge of the liquid. With ferric chlorid, it yields, when fresh, a bright green color and, after keeping, a brownish color. The solution in dilute alcohol, when kept for a few days, becomes a grass-green color. It contains about 1.3 per cent. of nitrogen. By prolonged shaking with acidulated water, it yields to the latter a substance which is precipitated by Mayer's reagent and the other alkaloidal precipitants. If the extraction of a benzol solution of this body with a 1 per cent. hydrochloric acid solution be continued until the aqueous shakings no longer respond to Mayer's reagent, the resin-like body that is left behind is physiologically inert, and contains no nitrogen. The nitrogenous body separated by this process represents about 9 per cent. of the original substance and is extraordinarily active, and responds to the usual tests for alkaloids.

It seems to us improbable that the resin and alkaloid which compose this body are simply mixtures. It will be remembered that Knebel<sup>16</sup> showed that caffein did not exist in kola-nut as free caffein, but in the form of a glucosid, to which he gave the name kolanin, which on decomposition yielded the alkaloid, glucose and an inert substance. A similar state of affairs is the most plausible explanation of the close correspondence that we have found between the physiological activity of a specimen of ergot and the proportion of this body contained in it. This fact will be considered in more detail later in the paper.

Although the lack of definite statement by Jacobi as to the chemical properties of his sphacelotoxin, and his unfortunately indefinite use of the terms chrysotoxin and sphacelotoxin, makes it impossible to assert positively the identity of sphacelotoxin and the substance we have separated by means of benzol, yet the fact that the two have the same range of solubilities, that they both turn green on standing, and that their physiological powers are at least comparable in degree, justifies us, we believe, in applying the term sphacelotoxin to this substance. As regards

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16. Knebel: *Die Bestandteile der Kolanuss*, Frankfurt, 1892.

the nitrogenous body which we have separated from our sphacelotoxin, we see no reason to doubt its identity with hydro-ergotinin (ergotoxin). In this connection it is interesting to note that in Dale's experiments, a dose of 1.3 mg. per kilo in a cat produced a marked rise of blood-pressure with vasomotor reversal; while our alkaloid produced in a dog in a dose of 1.6 mg. per kilo, a sustained rise of 34 mm.

TABLE 2.—PROTOCOLS TO SHOW COMPARATIVE ACTIVITY OF PRINCIPLES SEPARATED FROM ERGOT

Time, Pressure.		EXPERIMENT I
0	100	Inject 0.6 mg. (per kilo) whole resin.
2	115	
4	124	
8	107	
Time, Pressure.		EXPERIMENT II
		Pregnant bitch; abdomen opened to observe viscera.
0	120	For past ten minutes no movements of uterus.
1	120	Inject 1.6 mg. (per kilo) of whole resin.*
2	154	Marked contraction of circular fibers of uterus.
3	150	Marked intestinal peristalsis.
5	19	
10	9	Intestinal peristalsis more violent.
Time, Pressure.		EXPERIMENT III
0	110	Inject 0.16 mg. (per kilo) of alkaloids.*
5	145	
10	143	
17	140	
Time, Pressure.		EXPERIMENT IV
0	88	Inject 0.2 mg. (per kilo) washed resin.*
1	86	
4	90	Inject 2.5 mg. washed resin.
6	96	

\* For convenience, the body extracted from ergot by benzol is referred to as "whole resin," although it must be remembered that it is not all the resinous matter of the drug. The term "alkaloid" indicates the nitrogenous body separated from this resin and "washed resin" the inert material left after separating the alkaloid.

#### BIOLOGICAL ASSAY

The first effort to standardize preparations of ergot by physiological means was made by Grünfeld,<sup>17</sup> who used the method devised by Kobert, based on the mortification of the comb and wattle of the rooster after large injections of this drug. The method, however, was not generally used for several years, until Houghton<sup>18</sup> published the results of some commercial applications in 1898, since which time it has been freely employed.

17. Grünfeld: Arb. d. Pharmakol. Instit. Dorpat, 1895, xi-xii, 295.

18. Houghton: Therap. Gaz., 1898, xiv, 433.

The theory of the cock's-comb test was that the ergot caused a violent contraction of the arteries, preventing the circulation in the comb and thus leading eventually to a dry gangrene, although as at present applied the final reaction is only transient darkening in color. There is, however, no convincing evidence that the interruption of the circulation is due to arterial spasm. If it were, one would expect an ischemia rather than a congestion. The fact that much larger doses are required to cause the bluing of the comb than are required to produce constitutional symptoms shows that the effect is a violent toxic one rather than a physiological one. According to our experience, one-third of the quantity which is needed to cause the least perceptible change in the comb is sufficient to cause diarrhea, that is, to stimulate intestinal peristalsis in the chicken, and if the relative susceptibility of the intestinal tract and the vasomotor system is the same as in the mammal, this dose would carry us into the toxic stage of circulatory depression. Von Recklinghausen<sup>19</sup> has shown that the cause of the gangrene is the formation within the arteries of a hyaline plug, but Kobert argued that this thrombus is formed on account of the slowing of the blood stream during the vascular spasm. This view, however, seems hardly tenable in the light of the experiments of Ellinger,<sup>20</sup> who produced similar changes in the cock's comb with cantharides and it seems to us that Ellinger's argument is reasonable that the formation of the thrombus is due to an irritant action on the intima.

From a practical standpoint the fifty experiments on the rooster which we have made have convinced us that this method of assay is too inaccurate to be of utility. In the first place, the individual susceptibility of different chickens is so great that the same animal must be used for comparative experiments with a standard preparation of the preparation to be tested. If this is done, it is evidently essential that the dose must not be large enough to cause permanent changes in the circulation of the comb; but lesser degrees of congestion are so difficult of comparison that it is almost impossible to determine accurately the final reaction. In certain roosters, for some unknown reason, we found it impossible, as have other experimenters, to produce any bluing at all of the comb or wattle. In one chicken that we experimented on, a dose of 2.1 c.c. of fluidextract of ergot gave rise to distinct constitutional symptoms, consisting of diarrhea, rapid breathing and excitement; the comb did not become bluish but seemed a little paler than normal. Larger doses produced more marked constitutional symptoms and a more pronounced blanching of the comb, but although we gave as high as 30 c.c.

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19. Von Recklinghausen: *Handbuch der allgemeinen Pathologie*, 1883, 349.

20. Ellinger: *Arch. f. exper. Path. u. Pharmacol.*, 1908, lviii, 437.

of the same preparation, no darkening of the comb occurred. It is of interest to note that two weeks after this last dose, the crop of the chicken separated as a dry, hard, blackish mass without suppuration. Grünfeld, as well as later investigators, has mentioned this local mortifying effect at the point of introduction of the drug whether administered by the mouth or hypodermically. The point we wish to bring out is that in two of three instances of local gangrene in our experiments, there was no gangrene of the comb or wattle.

On account of the uncertainty of the cock's-comb reaction, we have not attempted to make any comparative tests with this and other methods of assay. Edmunds, however, experimented with a preparation which produced a typical reaction in the rooster but was inert when tested on the uterus.

In 1908, Edmunds<sup>21</sup> published a method of assay, based on the quantity of ergot required to produce contractions in the uterus of a cat. We believe, that with proper precaution, this method would be capable of giving reliable results, but there are a number of factors which make it, in our opinion, less desirable than the one we have to suggest. There are three objections to this method which seem to us of practical importance: In the first place, there is no distinct end-reaction to show how vigorous shall be the uterine contractions which will indicate the action of the drug; secondly, it has been proven that there is a distinct difference in the susceptibility of the multiparous and nulliparous uterus; and finally, it doubles the difficulty of obtaining test animals.

We may mention one other method, which has been used by Dale, in testing certain preparations from ergot. The Dale method is based on the observation that after the injection of certain principles derived from ergot, a dose of adrenalin causes a fall of blood-pressure instead of a rise; this he calls the vasomotor reversal. This vasomotor reversal is apparently not characteristic of ergot itself; Cronyn and Henderson found, as did we, that using the crude drug, the action was extremely uncertain. It is, therefore, not available for standardizing ergot.

We have used a method based upon the amount of elevation of the blood-pressure caused by the injection of a standard dose of ergot.<sup>22</sup> The

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21. Edmunds, C. W., and Roth, G. B.: *Physiologic Assay of Nitroglycerin Tablets, Digitalin Tablets and Fluidextract of Ergot*, Jour. Am. Med. Assn., 1908, li, 2130.

22. Since writing this paper we have seen a brief article published in 1905 (*Pharm. Jour. and Tr.*, 1905, lxxv, 157), of which we were previously unaware, by W. E. Dixon, containing the statement that he found the effect on blood-pressure to be a satisfactory means of standardizing ergot, but does not describe the details of the method employed. This communication of Dixon's antedates our first paper on this subject more than three years.



objection which has been raised against vasomotor tests of the drug on the ground that it is mere assumption to claim that a specimen active in regard to the circulation is equally so to the uterus, is, in the light of recent research, untenable. As has been shown above, the characteristic effect of ergot is a stimulation of all un-striped muscle tissue of the body, and the changes in the circulation, in the intestines and in the uterus are but a part of one general action. All of those substances which have been suggested by various writers as the active principle of ergot have produced stimulation of blood-vessel as well as uterus, with the exception of Vahlen's clayin, which there is strong reason to believe is not active. From a scientific standpoint there is no choice between a uterine and circulatory test for the drug; the preference must be made on purely utilitarian lines; which is the simpler and which yields the most reliable results. We shall consider the accuracy of results after description of our method.

The first thought in estimating the strength of the drug through its effects upon the circulation would be to compare the effects of the specimen being tested with the effects of a standard preparation in the same animal, as is done, for instance, with adrenalin. This in the case of ergot, however, is impossible because the drug lingers for so long in the system. We have already noted that the blood-pressure may remain high for at least two hours after the injection of a single dose, but even after the pressure has returned to the normal apparently there still remains some of the drug in the system, for we have found that the effects of a second dose of the same preparation cannot be compared to the effects of the first dose even if the pressure has returned to normal in the interval between the two injections. In all the experiments quoted in this paper we have considered only the effects of first doses.

Another method which would seem obvious, would be to ascertain the amount of drug necessary to produce a certain arbitrary rise in the blood-pressure in a series of animals. Our early experiments were carried out with this idea, but we were forced to abandon it because certain samples produced no rise at all, but especially because the amount of elevation did not vary according to the size of the dose. A dose of 0.12 gm. per kilo would produce as high a rise as double or treble or even four times this quantity. This point we shall consider later, but we will call attention here merely to Table 3, which shows the results of some of our early experiments bearing upon this fact.

Having demonstrated that the degree of action bore no relation to the size of the dose, we next carried out a series of experiments to determine whether the response was constant in different animals for the same dose

of the same preparation. The idea was to adopt a standard dose and measure the activity of the preparation by the rise of blood-pressure which followed the injection of this quantity.

TABLE 3.—EXPERIMENTS TO SHOW THAT EFFECTS DO NOT VARY WITH THE DOSE

Sample.	Dose per kilo.	Maximum rise in mm.	Sample.	Dose per kilo.	Maximum rise in mm.
P. D. No. 1....	0.10	35	H. K. M....	0.12	6
	0.16	77		0.20	21
	0.36	32		0.32	27
P. D. No. 2....	0.13	25	Lilly .....	0.07	24
	0.24	20		0.24	12
	0.48	20		0.41	41
Squibb No. 1..	0.14	24			
	0.29	62			
	0.33	44			
	0.34	52			
	0.35	45			

After some twenty experiments, we came to the conclusion that although there was some general agreement in the amount of elevation of the pressure, it was not close enough to be satisfactory for quantitative work (see Tables 3 and 4). A close examination of our tracings, however, showed that in those instances in which the pressure had ascended abnormally high it was not so well sustained as in those in which the first rise had been less striking; in other words, there was a tendency for a closer correspondence some time after the injection of the drug than immediately after. Our experience led us, in a previous paper,<sup>23</sup> to adopt, empirically, ten minutes after the injection as the period yielding the most constant results. Since the publication of this communication, however, further evidence has convinced us that it is necessary to take into consideration the total rise over the whole ten minutes, so that at present our figure of physiological activity is obtained by using the primary rise which follows immediately after the injection and the elevation at five and ten minutes after the injection respectively, and taking the average of the three figures, which gives us approximately the average rise for ten minutes after the injection.

TABLE 4.—SHOWING THE MAXIMUM RISE PRODUCED BY DOSES OF 0.33 GM. PER KILO

P. D. No. 2.	Squibb No. 1.	S. K. F. No. 1.
70 mm.	47 mm.	40 mm.
27 mm.	45 mm.	50 mm.
75 mm.	50 mm.	65 mm.
57 mm.	62 mm.	
89 mm.	55 mm.	
57 mm.	42 mm.	

23. Wood and Hofer: Univ. Penn. Med. Bull., 1909, xxi, 348.

in Table 1 are the results of eighty-four tests of twenty-two samples of ergot. It will be noted in this table, that in 55 per cent. of the experiments, the average rise is within 5 mm. of the average for the whole series with each preparation. For instance, with preparation Squibb No. 2, there are five tests, and of these, the average of the whole group being 36.6 mm., the lowest rise was 28 and the highest was 42 while the other three were less than 4 mm. from the total average of the series. If we extend the limit of error to 10 mm. departure from the average, only 20 per cent. will be outside the limit. It is evident, therefore, that where we have three closely agreeing results, the average of the series will almost certainly be within 5 mm. of the theoretically correct figure for that specimen.

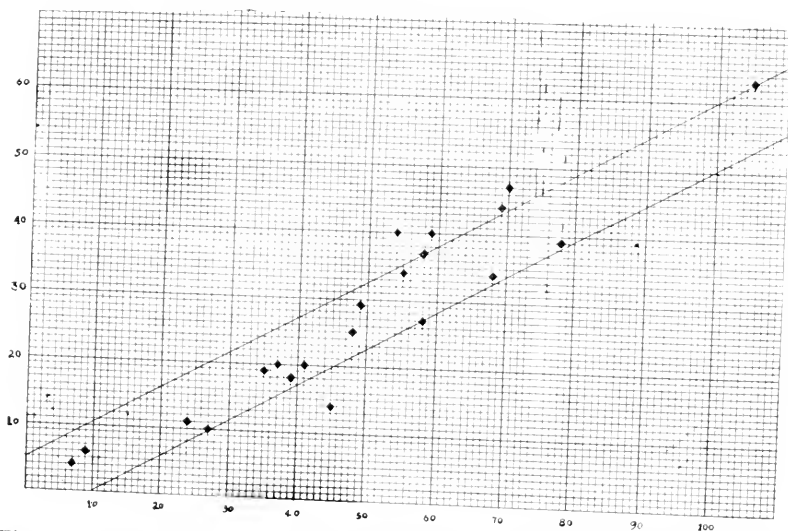


Fig. 4. Results of comparative physiological and chemical assay of various samples of ergot. Figures on abscissa = parts sphacelotoxin per 10,000; figures on ordinate = rise of blood-pressure in millimeters of mercury. Oblique lines represent variations of 5 mm. in the rise of pressure.

One surprising fact is that the activity of the specimen bears no relation to the size of the dose which is required to produce the maximum rise for that sample; the rise of pressure caused by any specimen of ergot is just as great after an eighth of a gram per kilo as after a fourth or even a half, no matter whether we are dealing with an inert or highly active sample. This is apparently so contrary to the accepted laws of pharmacology that we were very loath to believe it, but our experience, covering now some two hundred tests, allows in our mind no doubt.

The truth of this statement may readily be seen by referring to Table 4. For instance, in preparation marked Squibb No. 2 F., we have doses ranging from 0.13 to 0.20 gm. per kilo: the highest pressure in this instance being produced by the smallest dose. In sample marked Retail No. 1, the doses range from 0.13 to 0.25 and the effects in each instance are practically identical. With retail sample No. 2, although the dose in one instance was as high as 0.55 gm., we obtained practically no evidence of stimulation of the vasomotor system. In a fluidextract which was made in our own laboratory, marked in the table Wood No. 1, the effects of 0.16 gm. were exactly the same as those of a dose of 0.24 gm.

It therefore becomes necessary to determine the dose which will produce the best results in the majority of animals. Of course, there will

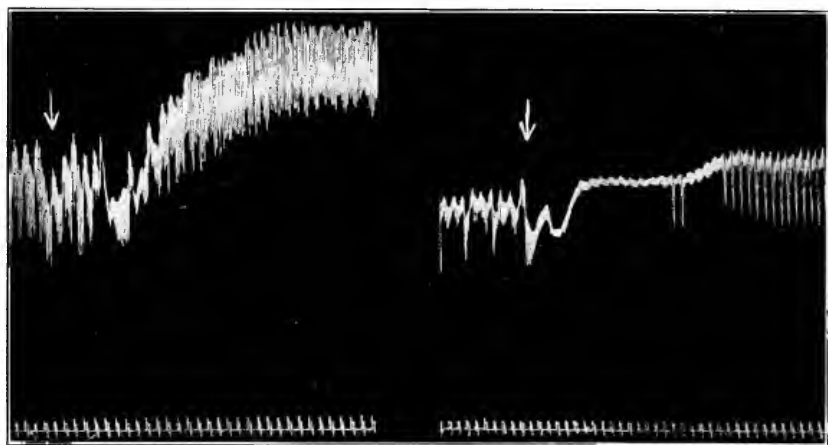


Fig. 5. Showing the deterioration in ergot when improperly kept. The tracing on the left shows the effect of a fluidextract of ergot which had been kept hermetically sealed; the one to the right shows the effect of the same dose of the same preparation after being exposed to the air for 46 days.

be more or less frequent individual variations in the susceptibility of dogs to ergot, so that what is the full physiological dose for one dog may be too small for a second and toxic for a third, but this error can be avoided by a means which we shall mention later. For the present, we wish to determine the dose for the average animal; this must be large enough so that in the majority of cases it will produce the greatest rise possible for that specimen of ergot, and small enough that it will not cause toxic effect in any considerable number of experiments. As evidence of a toxic action, we have taken the fall of pressure to a point

below normal within a period of ten to fifteen minutes after the intravenous injection of the drug.

We have as available for determining the limit of probable toxicity, the results of 111 experiments which may be tabulated as in Table 5.

TABLE 5.—PER CENT. OF TOXIC EFFECTS AFTER DOSES OF VARYING SIZES

	No. experiments.	Fall below normal. Per cent.
0-0.10 gm. per kilo.....	2	0.
.10-15 gm. per kilo.....	30	10.0
.16-20 gm. per kilo.....	49	16.3
.21-25 gm. per kilo.....	9	22.2
Above 25 gm. per kilo.....	21	38.1

It will be seen that with doses ranging between 0.10 and 0.20 gm. per kilo, we have toxic effects in about 13 per cent. of the experiments, and that above the latter limit, the toxic results occur in a much larger number of instances.

To determine the low limit, that is, the smallest dose which is likely to produce the full physiological effect, we have compared the results of a second injection of the same dose at an interval of not less than ten minutes after the first injection. If the blood-pressure is higher above the normal after the second dose than after the first dose, we consider that the full physiological action was not produced by the first dose. We give a table covering the results of 52 experiments bearing upon this point. In this table, it will be noted that with doses of less than 0.10 gm. in every instance the blood-pressure was driven higher by a second dose; while with doses ranging between 0.10 and 0.20 gm. in 88 per cent. of cases the first dose produced full physiological action.

It is evident from these two tables that, most generally, efficient doses of ergot will be equivalent to about 0.15 gm. per kilo of body weight.

TABLE 6.—PER CENT. OF INSTANCES IN WHICH SECOND DOSE CAUSED A RISE TO A POINT HIGHER THAN THAT PRODUCED BY FIRST DOSE

	No. of experiments.	Higher after second dose.
0-0.10 gm. per kilo.....	4	100.0 %
.11-15 gm. per kilo.....	19	26.3 %
.16-20 gm. per kilo.....	9	12.5 %
Above 20 gm. per kilo.....	20	5.0 %

#### DESCRIPTION OF METHOD

Our method as finally worked out is as follows: A dog is given hypodermically from 0.02 to 0.06 gm. morphin sulphate according to its size, and after the morphin has had time to act, is tied down and lightly etherized. The carotid artery is connected with a mercury manometer

and the jugular vein prepared for injection. The animal is then allowed to recover from the ether, the blood-pressure not being considered normal until it has remained at a constant level for at least ten minutes after withdrawing the anesthetic. A dose of the preparation under question is then injected, equivalent to approximately 0.15 gm. of ergot per kilo and the pressure observed for fifteen minutes. At the end of that time, a second dose should be administered in order to ascertain that the full effects have been brought out by the first injection. After watching the effects of the second dose for ten minutes the dog is killed, usually by injecting chloroform into the vein.

To obtain the results which we have described above, there are certain sources of error which experience has taught us must be sedulously avoided. Foremost among these, we wish to emphasize the necessity of the completeness of the recovery from the anesthetic before the administration of the drug. Not only are there likely to be changes in the blood-pressure during the convalescence from anesthesia, so that it is impossible to establish the norm accurately, but we have found, as have also Cronyn and Henderson, that the effects of ergot are very frequently atypical if any large quantity of ether is still circulating in the system. (Whether Henderson's anesthesia by intracerebral injection of magnesium chlorid would be available for this purpose we cannot say positively but would think it, *a priori*, improbable). In order to avoid fallacies from ether, we advise that the anesthesia be as light as compatible with prevention of suffering during the operation, and that the blood-pressure be observed at intervals until it has remained at the same level for ten minutes, before injecting any ergot.

While, of course, the perceptive centers of the dog are much benumbed by the morphin, we have found that in many cases there is a marked circulatory response to psychical influences as shown by alterations in the blood-pressure from whistling or calling. For this reason, complete silence, especially the avoidance of conversation and sudden noises, during the experiment is essential.

Our results in summer indicate strongly that when the room temperature is too high, the results are not altogether trustworthy. Into this question we have not gone in detail, but would not have much confidence in assays made in a room with a temperature of more than 25 C. (77 F.)

Several other factors which are usually believed to have an influence on the effects of drugs deserve a word or two of mention. Age appears to be a factor only in so far that immature animals are more susceptible to the drug, so that toxic effects are almost the rule with pups. We could observe no difference from sex. The sizes of our dogs have ranged from

4 to 20 kg. in weight, but with doses proportional to weight, we could see no distinction. The breeds were of all kinds, with a large preponderance of mongrel, the ordinary street dogs of a large city.

TABLE 7.—RESULTS OF 84 TESTS OF 22 SAMPLES OF ERGOT

Preparation.	Dose.	Primary	5 Min.	10 Min.	Average	
Squibb No. 1...		rise.	rise.	rise.	rise.	
	.33	47	32	2	27	
	.34	50	33	8	30	
	.35	45	33	9	29	
Average ...	.34	47.3	32.7	6.3	28.7	
Squibb No. 2...	0.05	10	5	4	6	Fresh
	0.13	56	39	30	42	
	0.15	50	....	30	40	
	0.16	55	40	25	40	
	0.16	40	....	25	33	
	0.26	35	25	25	28	
Average ...	0.172	47.2	34.7	27	36.6	
Squibb No. 2...	0.16	40	....	25	33	Sealed bottle two months old.
	0.17	64	59	35	53	
	0.18	clot	32	17	32	
	0.18	50	....	15	32	
	0.18	34	34	25	31	
	?	75	....	25	50	
	0.18	90	....	10	50	
Average ...	0.175	58.8	41.7	21.7	40.5	
Squibb No. 2...	0.15	15	....	0	7	Open bottle two months old.
	0.17	51	....	11	31	
	0.19	20	21	15	19	
	0.33	32	23	6	20	
Average ...	0.21	29.5	22	8	19.5	
Squibb No. 3...	0.13	46	....	27	36	Fresh.
	0.16	45	....	30	37	
Average ...	0.145	45.5	....	28.5	37.0	
Squibb No. 3...	0.13	42	25	5	24	Sealed bottle four months old.
	0.16	34	31	23	29	
	0.16	26	27	25	26	
	0.17	43	28	18	30	
	0.18	43	36	29	36	
Average ...	0.16	37.6	29.4	20	29	
Squibb No. 4...	0.13	70	25	12	36	Sealed.
	0.14	69	69	60	66	
	0.15	48	46	49	48	
	0.15	49	41	15	35	
	?	59	54	43	52	
Average ...	0.143	59	47	35.8	47.4	

TABLE 7.—Continued

Squibb No. 5...	0.13	48	33	26	36	
	0.15	79	16	25	40	
	0.18	45	51	35	44	
Average ...	0.153	57.3	33.3	28.7	40	
Retail No. 1....	0.13	23	20	7	17	
	0.22	35	10	8	18	
	0.25	28	27	9	19	
Average ...	0.175	29	19	7.5	18	
Retail No. 2....	0.13	10	0	0	3	
	0.40	10	5	0	5	
	0.55	15	5	0	7	
Average ...	0.36	11.7	3	0	5	
S. K. F. No. 1..	0.14	31	30	28	30	Fresh
	0.33	50	48	35	44	
	0.33	65	65	49	60	
	0.51	65	60	40	55	
Average ...	0.328	52.8	50.8	38	47.3	
S. K. F. No. 1..	0.16	36	22	16	25	Kept corked.
	0.19	22	11	10	14	
	0.19	26	....	15	20	
	0.29	22	15	12	16	
Average ...	0.208	26.5	16	13.3	18.8	
S. K. F. No. 1..	0.21	42	14	20	25	Sealed bottle.
	0.22	30	24	20	25	
	?	42	31	20	31	
	?	32	11	10	18	
Average ...	0.215	36.5	20	17.5	24.8	
S. K. F. No. 2..	0.10	33	....	6	19	Sealed bottle five months old.
	0.14	48	43	34	42	
	0.16	44	42	21	36	
	0.16	53	36	8	32	
	0.16	58	46	29	44	
Average ...	0.155	50.8	41.8	23	38.5	
S. K. F. No. 2..	0.16	30	13	11	18	Open bottle four months old.
	0.16	12	6	clot	....	
Average ...	0.16	21	9.5	11	13.8	
S. K. F. No. 2..	0.19	28	27	24	26	Open bottle one month old.
	?	34	30	3	23	
Average ...	0.19	31	28.5	13.5	24.3	



TABLE 7.—Continued

Cook No. 1.....	0.14	34	27	18	26	Fresh.
	0.14	44	....	24	34	
	0.14	30	....	15	22	
	0.16	86	....	66	76	
	0.21	15	....	6	11	
Average ....	0.158	41.8	27	25.8	33.8	
Cook No. 1.....	0.15	38	34	18	30	Sealed bottle one month old.
	0.16	84	74	53	70	
	0.17	63	....	31	47	
Average ....	0.16	61.7	54	32.7	49.0	
Cook No. 1.....	0.12	30	35	38	34	
	0.13	40	39	27	35	
	0.13	52	22	22	32	
Average ..	0.127	40.7	32	29	33.7	
Cook No. 2.....	0.17	37	17	7	20	
	0.18	15	9	6	10	
	0.17	7	2	0	3	
Average ..	0.175	19.7	9.3	4.3	11.0	
Wood No. 1...	0.16	46	35	22	34	
	0.17	40	....	13	27	
	0.24	45	30	25	33	
Average ..	0.19	43.7	32.5	20	31.3	
Special .....	0.14	15	4	2	7	
	0.14	12	....	0	6	
	0.20	36	20	16	24	
	0.23	37	34	22	31	
	?	30	25	18	26	
Average ....	0.178	26	20.8	11.6	18.8	

## CHEMICAL ASSAY

The only methods employed for the chemical assay of ergot have been various modifications of that of Keller, which is based on the percentage of total alkaloids present. As far as our reading goes, there is no experimental evidence to show that the figures obtained by Keller's method of assay bear any relation to the physiological activity of different specimens of ergot. The paper of Dohme and Crawford, which is sometimes quoted as demonstrating the value of Keller's test, is open to several serious objections. It really proves nothing beyond the fact that one can obtain from ergot physiologically active alkaloids. Vanderkleed found that the relationship between the percentage of alkaloids and the activity of ergot when tested by the cock's-comb method is extremely

precarious. It has been pointed out by Barger that the fallacy of Keller's method resides chiefly in the fact that the alkaloids extracted consist of a mixture of the active hydro-ergotinin and the inert ergotinin, and that as there is no method of separating these alkaloids, the resultant figures are untrustworthy.

In the course of our experiments in the biological standardization of ergot, we were struck by the fact that those samples of fluidextract which gave but little precipitate on the addition of water were uniformly of low potency; this led us to investigate the possible relation between the percentage of resinous matters and the activity of the drug. After experimenting with various solvents, we finally decided on the following method: Take 10 c.c. of fluidextract of ergot, add 20 c.c. of water, shake with repeated portions of 10 c.c. each of benzol, until the latter comes away colorless; unite the various portions of benzol in a tared dish, evaporate over a water bath and dry at a temperature of 37° C. to constant weight. We may remark in passing that almost uniformly very troublesome emulsions are formed; these can be most readily broken up by the method suggested by Dunn, of adding filter paper to the emulsion.

We have already described the chemical nature and physiological properties of the body which is obtained by benzol extraction. We wish, at this place, simply to emphasize the fact that the benzol extractive does not represent the total resin of ergot; the proportion of the water-insoluble substances which are dissolved by the benzol varies greatly in different specimens.

Whether or not our ideas of the nature of this substance are correct, we are well satisfied that the amount present is an accurate indicator of the activity of the fluidextract of ergot. We give herewith (Table 8) the results of comparative physiological and chemical assays of twenty-one samples of fluidextract,<sup>24</sup> ranging in physiological activity from 4 to 63, covering the whole gamut of possible degrees of power. It will be noted that the percentage of benzol extractive increases regularly as the physiological activity becomes greater. There are, as might be expected, one or two slight deviations from mathematical exactitude, but these are mostly well within the limit of error. In the case of the sample marked Special, two of the physiological tests differed very widely from the rest of the series (see Table 8). Excluding those two experiments, the physiological figure would be 27 instead of 19.

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24. The sample labeled Wood No. 2 is a 50 per cent. tincture, but is calculated to correspond to fluidextract strength.

TABLE 8.—RESULTS OF COMPARATIVE PHYSIOLOGICAL AND CHEMICAL ASSAYS OF 21 SAMPLES OF ERGOT

Preparation.	Per cent. of Sphacelotoxin.	Rise of Blood-pressure.
Sq. Exp. ....	0.07	4
Warner ....	0.09	6
Retail No. 4...	0.27	10
Cook No. 2....	0.24	11
S. K. F. No. 1 (C)...	0.35	19
Squibb No. 2 (O)...	0.37	20
Cook No. 1 (O)....	0.39	18
Wood No. 2....	0.42	20
S. K. F. No. 2 (O)...	0.45	14
S. K. F. No. 1 (S)...	0.48	25
Squibb No. 3 (S)...	0.49	29
Cook No. 1 (S)....	0.55	34
Squibb No. 5....	0.54	40
Special ....	0.58	19
Squibb No. 3 (F)...	0.58	37
Squibb No. 2 (S)...	0.59	40
Cook No. 1 (F)....	0.68	34
Squibb No. 4 (C)...	0.69	44
Squibb No. 4 (S)...	0.70	47
S. K. F. No. 2 (S)...	0.78	39
S. K. F. No. 2 (F)...	1.05	63

For easier comprehension of these results, we have plotted them in a diagrammatic form: in Figure 4, the abscissa represents parts per ten thousand of sphacelotoxin and the ordinate millimeters of rise of blood-pressure. We have drawn on this figure, two parallel lines, representing variations of 5 mm. in the blood-pressure above or below the average, which is the limit of accuracy we claim for our method of physiological assay. In this figure, four specimens are slightly outside of these limits. Of these, one is the sample labeled in our Table S. K. F. No. 2 (O); of this sample, unfortunately, we have but two physiological tests, and one of these is not complete on account of a clot at the end of the ten minutes, so that we can place comparatively little reliance on the physiological figure. Of the other four samples which fall without the limits mentioned, only one is more than 3 mm. of pressure outside these limits, so we feel justified in claiming that there is a marked degree of parallelism between the physiological activity of the drug and the percentage of sphacelotoxin.

Another fact which is strongly corroborative of the value of this method of assay is that in specimens which have deteriorated from long keeping, the diminution in the amount of sphacelotoxin runs closely parallel to the loss of physiological power (see Table 12). Thus, S. K. F. No. 2, when fresh, gave a chemical assay of a little over 1 per cent. and caused a rise of blood-pressure of 63 mm. A sample of this fluid

extract kept hermetically sealed, showed six months later a sphacelotoxin content of 0.81 per cent.; the same preparation, left uncorked, fell in its chemical assay from 1.05 to 0.45, and in its physiological figures from 55 to 13. Similar parallelism may be noted in the case of Squibb No. 4, Squibb No. 3 and Cook No. 1.

A further confirmation of our beliefs we are enabled to offer through the courtesy of E. R. Squibb and Son. This firm prepared for us two concentrated preparations from the same sample of crude ergot, one of which contained 0.5 per cent. of alkaloid by Keller's method and 0.7 per cent. of sphacelotoxin; the other preparation contained the same amount of alkaloid but yielded 4.0 per cent. of sphacelotoxin. The former preparation, rich in alkaloid, when injected into the dog in doses of 22 mg. per kilo. caused a rise of 14 mm. in the blood-pressure, and in a dose of 53 mg. gave a rise of but 24 mm. The other preparation, which contained a high percentage of resin, gave in doses of 23 and 29 mg., 40 and 45 mm. rise respectively.

TABLE 9.—COMPARISON OF TWO PREPARATIONS FROM THE SAME SAMPLE OF ERGOT

Preparation.	Per cent. alkaloids.	Per cent. sphacelotoxin.	Dose gm.	Rise of pressure.
A .....	0.55	0.70	0.022	13
			0.053	24
B .....	0.60	4.04	0.023	34
			0.029	41

Further evidence of the value of this method of assay is derived from a study of the comparative activity of the matter extracted by benzol and the residue left behind after benzol extraction. In Table 10 are the protocols of three experiments made with different portions from fluidextract Cook No. 1. It will be seen, that while large doses of the watery residue produced a slight rise of the blood-pressure, the effect was in no way comparable to the strength of the whole fluidextract. Thus in Experiment 2, the injection of an amount of the mare of the fluidextract equivalent to 0.12 gm. of the original fluidextract produced a rise of 10 mm.; 0.15 gm. more of the same preparations produced a maximum rise of 29 mm. above the normal (we did not wait long enough to determine how well this rise would be maintained), but an injection of the benzol extract from the same preparation representing 0.15 gm. of ergot produced a maximum rise of 55 mm. above the normal, or 26 mm. above the point at which the injection was made.

The activity of a number of these watery residues in comparison with the activity of the whole fluidextract is presented in Table 11.

TABLE 10.—ACTIVITY OF WATERY RESIDUES IN COMPARISON WITH THAT OF BENZOL EXTRACT

Time. Pressure.		
Fluidext. Cook No.1.		
0	97	Inject watery residue equivalent to 0.15 gm. fluidextract.
1	105	
4	97	
15	100	Inject 0.15 gm. more of watery residue.
16	108	
19	100	Inject benzol extract equivalent to 0.21 gm. fluidextract.
22	123	
28	119	
35	128	
Cook. No. 1.		
0	95	Inject 0.12 gm. watery part.
2	105	
4	105	Inject 0.15 gm. more (watery part).
8	124	
9	...	Inject 0.15 gm. benzol soluble.
10	150	
12	145	
Cook No. 1.		
0	114	Inject benzol extract—0.28 gm. ergot.
2	142	
5	140	
6	...	Inject benzol extract—0.11 gm. ergot.
8	142	
12	145	
13	...	Inject watery residue—0.17 gm. ergot.
15	153	
17	145	
19	140	

TABLE 11.—ACTIVITY OF WATERY RESIDUES IN COMPARISON WITH THAT OF FLUID EXTRACT

Sample.	Part used.	Dose.	Max. rise.	Av. rise.
Squibb No. 3.....	Fluidextract *	0.15	45	37
Squibb No. 3.....	Watery residue	0.17	25	12
Squibb No. 5.....	Fluidextract *	0.15	57	40
Squibb No. 5.....	Watery residue	0.17	4	1
Squibb No. 5.....	Watery residue	0.23	10	7
Cook No. 1.....	Fluidextract *	0.16	42	34
	Watery residue	0.15	8	4

\* Averages from Table 7.

The possession of a slight degree of activity by the residue is not, in our opinion, a potent objection to the method. The United States Pharmacopeia recommends the assay of opium for its morphin, neglecting other active alkaloids which are present, and it must certainly be true that the residue left behind in the opium after extraction of the morphin is not entirely inert; in the same way, *nux vomica* is assayed for its strychnin, entirely overlooking the presence of brucin. It is apparent, therefore, that chemical assay may be satisfactory even if a slight degree of potency remains in the marc.

We have met, however, with a more serious objection to our method of chemical assay in testing preparations other than the fluidextract. For instance, Squibb sent us an experimental preparation of ergot which showed 0.45 per cent. of Keller cornutin and 0.21 per cent. of sphacelotoxin. This percentage of sphacelotoxin corresponds to physiological activity of about 10, yet a dose of 0.16 c.c. of this sample produced a rise of 53 mm. It is evident, therefore, that it is possible to obtain a watery solution of ergot which contains so large an amount of para-hydroxyphenylethylamin, or some other principle, as to produce a considerable rise in the blood-pressure although the sphacelotoxin content may be very low; but also it is possible to obtain a preparation from opium, almost free from morphin, which would be highly depressant to the respiratory center through a large amount of codein. We would point out that while it may be possible to make watery preparations of ergot which will give, when tested by the blood-pressure method, high figures, yet such preparations are made at a great waste of ergot. For instance, the preparation just mentioned was supposed to be four times the strength of the fluidextract, and yet when tested physiologically it was in the same class with an active fluidextract. In other words, there had been a loss of ergot amounting to 70 per cent. We have found that all those watery preparations which we have examined have been far below the strength which the manufacturers claimed for them.

Another exception to our assay method is in the case of preparations made with glycerin, as for instance, by the formula suggested by G. M. Beringer.<sup>25</sup> We have examined two such preparations, one made by Mr. Beringer himself and the other by Professor Cook. One of these gave a physiological figure of 21 but yielded only 0.19 per cent. of sphacelotoxin. The other gave a rise in blood-pressure of 15 mm. but only 0.08 per cent. of benzol extractive.

#### CAUSES OF THE POOR QUALITY OF ERGOT

There has long been great dissatisfaction among clinicians with the quality of ergot which is available for practical use. Our investigations show that this distrust is well grounded. Of four preparations which we have obtained from the most reputable retailers in Philadelphia, the most active gave an average sustained rise of only 18 mm.; the other three gave respectively 10, 11 and 5 mm. If this is what may be expected from the better class of retail pharmacists, it is apparent that the fluidextract of ergot as ordinarily dispensed on prescriptions is nearly inert.

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25. Beringer: *Proc. Am. Pharm. Assn.*, 1908, lvi, 981.

There are four possible causes for the lack of activity of commercial samples of preparations of ergot: (1) original inertness of the drug, (2) changes taking place in the crude drug, (3) improper methods of extraction, (4) changes taking place in the preparations after manufacture. We shall consider these four causes seriatim, and endeavor to find out the most important ones and to point out a remedy for the present undesirable condition.

As to differences in the activity of a fresh drug owing to possible influences of climate, soil, and so forth, our evidence is comparatively meager. It is so difficult to obtain authentic samples of the crude drug from different localities that it is almost impossible for investigators to accurately determine this point. Our sole evidence is based upon three samples of ergot. Through the courtesy of H. K. Mulford and Company, we were provided with a sample of German ergot and one of Spanish ergot. We found the Spanish more active than the German ergot.

As to the deterioration which takes place in crude ergot, this may be the result of one of two causes, the attacks of insects to which the drug is peculiarly liable, or spontaneous chemical changes taking place in the drug. Grünfeld tested a sample of crude ergot by the cock's-comb method at varying intervals. He found it required, in October, twice the dose that it did in August to produce the same degree of reaction, and that in February it required eight times this dose; in April twelve times the dose, and by the following June no dose would produce the reaction. This would indicate a deterioration in the first two months of keeping, at the rate of 6.2 per cent. a week; in the first six months of keeping, a rate of 3.5 per cent. per week; and in nine months of keeping, a rate of 2.8 per cent. a week. We attempted to make an investigation into this point, but owing to various obstacles, the results are of no value.

Grünfeld does not mention how the ergot was kept, except that it was powdered. Although the experiments which we made as regards the keeping quality of crude ergot do not throw any light on the rate of deterioration, they are at least suggestive as to the influences of different methods of storing. On November 1, 1908, we received from Smith, Kline and French, a sample of fluidextract (marked in our tables as S. K. F. No. 1) and also a sample of the ground ergot from which this fluidextract was made. The ground ergot was divided into three portions, one of which was kept in a paper box, the second hermetically sealed in a glass bottle, and the third was dried for forty-eight hours at a temperature of 37° C. and then hermetically sealed. At the time this ergot was received we had not yet worked out our method for a chemical assay of the drug and the figures on this point are therefore lacking.

The physiological test which was made of this fluidextract at the time it was received showed a rise of 47 mm., but this figure is evidently too low, when taken in the light of the chemical studies later made of the ground ergot. The three samples of crude ergot were made up into fluidextracts by Professor Cook six months later and yielded the following percentages of sphacelotoxin:

Sealed, 0.81.

Dried and sealed, 1.10.

Kept in paper box, 0.93.

These figures indicate that the best method of keeping crude ergot is to dry it at low temperatures and then to protect it from atmospheric influences by keeping it hermetically sealed.

If crude ergot loses strength as rapidly as the figures of Grünfeld indicate, it is evidently important to determine the length of time which ordinarily elapses between the harvesting of the ergot and its manufacture into fluidextracts. In the present condition of the ergot business, both in Europe and in this country, it is almost impossible to know definitely the age of any individual sample of ergot. Some of the larger manufacturers have their own agents in the ergot districts of Europe, and are therefore able to know within reasonable probability of the freshness of their supply; but the smaller manufacturers who have to rely on general importers of the drug are entirely at the mercy, first, of the European dealers, who will hold over from year to year any of the drug not sold immediately after its collection, and also of the jobbers in this country who sell, of course, any stock that they happen to have on hand. We have a sample of ergot, obtained from a London exporter by H. K. Mulford & Co., which was received in London in 1904, with the statement that it had been kept in cold storage for three years, and when it reached our hands in 1908, was therefore at least seven years old. It was thoroughly worm-eaten, but in its general appearance vaguely suggested ergot. In the letter which accompanied it, was the naive statement by the exporter that "if sifted, it would look presentable, but could be salable at current prices only if a scarcity came along or if wanted for a cutting contract for some institution."

As bearing on the quality of ergot which is made up into fluidextracts, it is interesting to note that of seven fluidextracts which were furnished us directly by the manufacturer, six reached a reasonable standard of activity; one specimen was practically inert.

Some years ago, Dr. E. H. Squibb had a fluidextract of ergot prepared by his firm, carried by a ship surgeon on a voyage around the world, and when, in the course of time it came back to him, he tested it



clinically and came to the conclusion that it was active. A similar observation to that of Dr. Squibb has been reported by Sharp<sup>26</sup> with a liquidextract of the British Pharmacopeia, which he found active after twelve months. Largely on the basis of Dr. Squibb's observation, the belief is prevalent among pharmacists that the fluidextract of ergot is a stable preparation, and that the cause of the poor quality of the drug on the market is owing to changes in crude ergot before manufacture.

We would point out, however, that such evidence is practically worthless. In the first place, there was no definite knowledge of how active the preparation of ergot was when manufactured and in the second place, no reliable information as to the activity at the end of the year. Clinical tests cannot be considered as scientific evidence in such questions.

We have, moreover, very convincing proof that the fluidextract of ergot is fully as unstable, if not more so, than the crude drug. The evidence of this, as well as of some points which bear upon the causes of this change, are summarized in Table 12. In this table, the samples S. K. F. No. 1 and Squibb No. 2, were received from the manufacturers before the chemical method of assay was worked out and for purposes of accuracy in relative strengths we have much more confidence in our chemical assay than in any physiological test. The figures which are given for these two samples for the percentage of sphacelotoxin represent the theoretical per cent. that a preparation giving the corresponding physiological figures should contain.

The method of studying the rate of change which took place was as follows: As each new sample of fluidextract was received it was divided into three portions, one of which was hermetically sealed in a bottle from which practically all the air had been excluded; the second was put away in a bottle simply stoppered with cotton to keep out the dust, thus permitting free exposure to the air; the third bottle was used for immediate tests. This third portion was opened from time to time to take out small quantities such as were needed, imitating closely therefore the conditions under which it would ordinarily remain on the pharmacist's shelf.

It will be noted that in the bottle exposed to the air, the loss of potency was comparatively rapid; in one case, as high as 5.5 per cent. each week, and in every instance the preparation had lost at least 50 per cent. of its active principle within a period of five months. On the other hand, those samples which were kept hermetically sealed lost their strength much more slowly; the most rapid of these, according to the

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26. Sharp: *Merk's Rep.*, November, 1908, p. 302.

table, being that of S. K. F. No. 1, which deteriorated at the rate of 2.3 per cent. a week. This figure, however, is hardly fair, because the sample had been kept in a bottle which was opened at various intervals for some two weeks before it was sealed; at the time of sealing this bottle the fluid-extract gave, in two experiments which were made at that time, a physiological activity of only 20, so that it is probable that change had already taken place in the preparation before it was removed from atmospheric influence. Leaving out this sample we find that the diminution in sphacelotoxin content ranged from 0.2 to 1.1 per cent. a week. In the cases of those bottles which were corked, but from which the air was not entirely excluded, the loss of potency was, as might be expected, midway between the sealed and the open bottles, showing an average of about 2.6 per cent. a week.

Another preparation made for us by Professor Cook may be quoted, although owing to an unexpected pharmaceutical problem the evidence is somewhat complicated. Professor Cook sent us, in May, a fluidextract, made according to the United States Pharmacopeia of 1880 and divided into two portions, one of which had been filtered after percolation, the other not. A portion of the unfiltered half, which contained 0.49 per cent. of sphacelotoxin, was sealed; the filtered portion which gave 0.34 per cent. was placed in an unstoppered bottle. Four months later, the sealed (unfiltered) gave 0.45 per cent. compared to 0.49 per cent. when fresh; the open bottle but 0.19 per cent., compared to 0.34 per cent. when fresh. It is interesting to note also that a bottle of the unfiltered sample which had been kept corked, but not hermetically sealed, gave at the same date 0.24 per cent. of benzol extractive.

TABLE 12.—TEST OF FLUIDEXTRACT OF ERGOT (COOK NO. 2) UNDER VARIOUS CONDITIONS OF FRESHNESS AND EXPOSURE

	Filtered.	Unfiltered.
Fresh . . . . .	0.34%	0.49%
Sealed . . . . .	.....	0.43% 21 weeks old.
Corked . . . . .	0.24%	0.37% 21 weeks old.
Open . . . . .	0.18%	..... 21 weeks old.

The evidence quoted above as to the changes which take place in the fluidextract of ergot throw much light on the causes of the poor quality of drug which is found in the retail market. In our opinion, the inertness of a retail fluidextract of ergot is due chiefly to the length of time elapsing between the manufacture of the fluidextract and its sale to the patient. Manufacturers are in the habit of storing away their fluidextract for varying periods of from three to nine months, in order to allow it to settle and become clarified. It then goes to the jobber, who

may store it for another six months or a year; it reaches the pharmacist at least one, and generally two years old, and stays on his shelf perhaps another year or two before it is dispensed to the patient. While a tightly corked bottle is almost hermetically closed, so that the fluidextract as stored by the manufacturer is protected against the deleterious influence of the atmosphere, it must nevertheless be remembered that the loss of strength, even in sealed bottles amounts to nearly 50 per cent a year on the average. It is evident, therefore, that it cannot be expected that a sample of fluidextract of ergot which has been kept for two or three years, even under the most favorable conditions, can possess a great deal of physiological power.

One other factor of importance from a pharmaceutical standpoint deserves mention, and that is the means which are used for extracting the activities from the drug. If our belief is correct that the most active ingredient of ergot is sphacelotoxin, it is evident that no watery preparations of ergot can thoroughly represent the drug. It is, of course, conceivably possible that by an elaborate process of manufacture, the sphacelotoxin could be decomposed and the alkaloid hydro-ergotinin obtained. This alkaloid, however, is itself almost insoluble in water, and according to Barger and Carr, the salts which it forms with the inorganic acids are likewise but slightly soluble, so that even by extracting the alkaloid in the free state, we can hardly hope to obtain a highly active preparation of ergot. Our experiments with various watery preparations of the drug bear out this deduction. We have tested physiologically three samples of this class of preparations, two of which are on the market and recommended for hypodermic administration, the third being an experimental product which was sent us by the manufacturer, who was attempting to obtain an active watery preparation of ergot. Not one of these three samples equaled the figures which were claimed for them by the maker. Two of them were almost absolutely inert, and the third, the label of which bore the statement that 1 c.c. equaled 4 gm. of ergot, was of about the strength of an ordinary fluidextract.

Our conclusions as regards the quality of ergot which is at the disposal of the physician may be summed up as follows:

1. Preparations of ergot obtained from retail pharmacists are almost universally far below the standard.
2. No preparation of ergot which does not contain considerable amounts of alcohol or some similar inorganic solvent can thoroughly represent the drug.

3. Starting with an active specimen of crude drug, a fluidextract freshly made, according to the process of the eighth revision of the United States Pharmacopeia, will furnish a potent preparation.

4. Both the crude drug and fluidextract deteriorate comparatively rapidly.

5. We would recommend, therefore, that all preparations of ergot should bear on the label the date of their manufacture, or at least the date beyond which the strength of the specimen cannot be trusted, as do the antitoxic serums, and should be preserved in small bottles, hermetically closed.

TABLE 13.—LOSS OF STRENGTH OF ERGOT BY KEEPING

How kept.	Physiological Test.	Sphacelotoxin.	How long kept wks.	Loss per week %
S. K. F. No. 1.				
Fresh .....	47	.70*	..	..
Sealed .....	25	0.48	14	2.3
Corked .....	19	0.35	14	3.6
S. K. F. No. 2.				
Fresh .....	63	1.05	..	..
Sealed .....	39	0.78	22	1.1
Corked .....	..	0.73	22	1.4
Open .....	14	0.45	20	2.8
Squibb No. 2.				
Fresh .....	37	0.60*	..	..
Sealed .....	40	0.59	7	0.2
Corked .....	..	0.45	25	1.0
Opened .....	19	0.37	7	5.4
Cook No. 1.				
Fresh .....	34	0.70	..	..
Sealed .....	49	..	5	..
Sealed .....	34	0.55	22	1.0
Open .....	18	0.39	6	7.4
Cook No. 3.				
Fresh .....	..	0.93	..	..
Corked .....	..	0.80	5	2.8
Corked .....	..	0.54	13	3.2
Cook No. 4.				
Fresh .....	..	1.10	..	..
Corked .....	..	0.75	13	2.4
Squibb No. 4.				
Fresh .....	..	0.95	..	..
Corked .....	..	0.69	12	2.3
Sealed .....	..	0.70	12	2.2
Experimental.				
Fresh .....	..	4.04	..	..
Corked .....	..	3.12	15	1.5

\* Estimated from the physiological figure.

## SUMMARY

The important facts brought out in this paper may be summarized as follows:

1. Ergot is a stimulant to all the unstriated muscle tissue of the body.
2. As a part of this general action there is a stimulant effect on the arterial muscles and probably also on the heart.
3. The action on the blood-vessels occurs after destruction of the vasomotor center and must be, therefore, the result of an effect on some portion of the peripheral vasomotor mechanism.
4. The degree of elevation of blood-pressure affords an accurate criterion of the activity of ergot and is, in our opinion, the most available method for the biological assay of the drug.
5. The active principle of ergot is an alkaloidal substance which occurs in the drug probably in chemical union with a resinous body. For the combination we suggest the retention of the name suggested by Jacobi of sphacelotoxin and for the alkaloidal substance the term applied by Kraft of hydro-ergotinin.
6. The percentage of sphacelotoxin varies accurately with the physiological activity of different specimens of ergot.
7. The percentage of sphacelotoxin in a fluidextract may be easily estimated by precipitating with water and extracting with benzol.
8. A fluidextract of ergot exposed to the air deteriorates extremely rapidly.
9. The deterioration of fluidextract of ergot may be much retarded by protecting it against contact with the air, but under the most favorable conditions there is a loss of strength approximating 10 per cent. a month.

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## THE UTILIZATION OF MILK-FAT BY AN ATROPHIC INFANT \*

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This paper furnishes a comparison of the results obtained from three observations made on an atrophic infant in which the absorption of fat was determined. Each observation lasted for three days, during which time the fat in the food and feces was determined.

For twelve days immediately preceding the first observation the infant was fed exclusively on human milk and the first observation succeeded this preliminary period without interruption. There was an interval of four days between the first and second observations and an interval of three days between the second and third observations.

During the first observation the infant was given 840 c.c. of breast-milk daily. During the second observation he was given 840 c.c. daily of a mixture of cows' milk containing approximately 3 per cent. of fat, 6 per cent. of milk-sugar and 1 per cent. of protein.

During the third observation the infant was given 840 c.c. daily of a mixture of cows' milk prepared with rennet, in which the percentages of fat, sugar and protein were approximately the same as during the second observation.

In the interval between the first and second observations the infant was fed on breast-milk. The reason for this will be referred to later. In the interval between the second and third observations he was given the same preparation of cows' milk treated with rennet that he received during the third observation.

Carmin was given at the beginning and end of each observation.

### PREPARATION OF THE FOOD

The fat in the cream that was used to prepare the cows'-milk mixtures was determined each day by the Babcock method, and the milk mixtures were prepared to contain approximately the desired percentage of fat. In each feeding-bottle 105 c.c. of the mixture were put, and, to avoid any chance of accidental spilling, the rubber nipples were fastened to the feeding bottles by strips of adhesive plaster. The infant received eight

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\* From the Biochemical Laboratory of the Harvard Medical School.

feedings in twenty-four hours. After each feeding the bottles were set aside until the next day, and then they were carefully rinsed and the fat in the rinsings was ultimately determined and the amount deducted from the total fat ingested. The amount of fat thus left was between 2.5 and 3 per cent. of the total quantity ingested.

In the third observation rennet was added to the milk to produce a finer subdivision of the fat. It appeared probable that, when cows' milk coagulated in more or less large and tough curds in the stomach, some of the fat which was enmeshed in these curds escaped digestion. If, therefore, the casein was coagulated before ingestion and was then passed through a fine-meshed sieve it was hoped that, though the fat would still remain mechanically bound to the casein, it would nevertheless be more finely subdivided and in this way its digestion would be favored.

In order to test this hypothesis, a mixture of cows' milk containing approximately 3 per cent. of fat was prepared and treated with rennet. On attempting to rub the coagulum through a sieve it was found that a considerable portion did not pass through and when this portion was squeezed between the fingers it was found to contain fine, hard particles. Professor Folin suggested that I add the rennet to the cream and prepare the mixture afterward.

The required number of ounces of cream to give 3 per cent. fat in the mixture was treated with rennet and it was then found that the entire coagulum could be pressed through the sieve and that, when squeezed between the fingers, it smoothed out without leaving hard particles. When mixed with the other ingredients of the milk mixture it settled to the bottom of the nursing-bottle, but with a somewhat larger aperture in the nipple, and by shaking the bottle occasionally during the feeding, very little remained behind. The amount of fat not ingested did not exceed that of the other periods.

#### COLLECTION OF FECES

The urine was not required for these observations, and a simple and effectual device was employed to prevent the admixture of urine and feces. The penis was put through a small opening in a sheet of rubber dam. The edge of the opening was fastened to the penis by a narrow strip of adhesive plaster. The rubber dam was pinned to the mattress on either side. Napkins were placed under and over the penis to absorb the urine.

In previous metabolism observations I made use of a Bradford frame to collect the feces and urine. This time I used a mattress such as the infant

was accustomed to. A suitable opening was made in the mattress, and the edges and several inches of mattress adjoining the edge on both sides were covered with rubber sheeting. A wire tray was fastened to the bed beneath the hole and close to the mattress. The wire tray held an oblong baking-tin a little smaller than the tray in which the feces were collected. These pans could be removed and replaced merely by sliding them in and out of the wire tray. During the observations the infant necessarily required more attention than usual and he was invariably cheerful when awake and slept normally.

#### METHOD OF ANALYSIS

During the three metabolism periods the fat in the food was determined each day by the Soxhlet method. Duplicate analyses were always made. Following the method of Black for the determination of oxybutyric acid<sup>1</sup> in the urine, plaster of Paris was added to 20 c.c. of the milk with constant stirring until the desired consistency was reached. It was then kept in the ice-chest until it could be analyzed. It crumbled readily when dry and afforded a very simple and convenient method for determining the fat in milk.

It was impossible by this method to make analyses of the rennet preparation agree, because of the unequal distribution of the fat. The difficulty was overcome by accurately weighing and measuring a considerable quantity of the rennet milk mixture, evaporating this to dryness, reweighing the dried residue and then extracting the fat from weighed portions. The total fat was calculated from this result. In this way very close controls were obtained. Sulphuric ether was used in the food analyses.

The fat was determined in the feces by a method recently devised by Professor Folin.<sup>2</sup> Some of the analyses of fat in the feces made last year by an older method did not check and so I discarded them all and applied to Professor Folin for a more accurate method. Thus far the method has not been tested in substances other than feces and here it appears to give very accurate results. Briefly described, Folin's method is as follows:

The fat is extracted with acid-ether, prepared by passing dry hydrochloric acid gas into anhydrous ether (the degree of acidity is controlled by titration). The extract is evaporated to dryness and allowed to stand over night under petroleum ether. The petroleum ether solution is carefully filtered, dried at a temperature under 100 C. and weighed as total fat. The fat is then dissolved in benzol, heated to boiling and titrated, while hot, against a standard solution

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1. Black, O. F.: Jour. Biol. Chem., 1908, v.

2. Folin: Jour. Biol. Chem., June, 1910.



of metallic sodium in absolute alcohol, using phenolphthalein as indicator. The end point is very sharply defined. When a large quantity of fatty acid is present it is advisable to continue the heat during titration. In this way the soap, which is formed, is kept in solution and permits of a sharp end point. If it is desired to estimate the fat which is present in the form of soaps, then anhydrous sulphuric ether is used for a first extraction with subsequent treatment with petroleum ether, etc., as described above, and this is followed by a second extraction with acid ether, etc., thus making two procedures which are identical, including the titration, except that two solvents are used. The first extraction removes the neutral fat and fatty acids; the second extraction removes the soaps which have been converted into fatty acids.

TABLE 1.—DETERMINATION OF FAT IN FECES

	Fat Ingested, gm.	Fat Absorbed, gm.	Dried Feces, gm.	Fat in Feces, Per Cent.	Neutral Fat in Feces, Per Cent.	Fatty Acid in Feces, Per Cent.	Fat Excreted, gm.	Fat Excreted, Per Cent.
1st Period, March 4 to 6,—								
Breast-milk .....	83.2	74.3	26.5	33.4	.06	27.4	8.8	10.6
2d Period, March 10 to 12,—								
Modified cow's milk .....	72.	63.7	15.3	54.4	.04	49.75	8.3	11.5
3d Period, March 15 to 17,—								
Modified cow's milk with rennet .....	72.3	64.	15.7	52.75	.05	47.75	8.3	11.5

## GENERAL CONSIDERATION

Before discussing the results of this observation it is necessary to consider certain points in connection with the feeding which bear directly on the results.

In the interval between the breast-milk and the first cows'-milk observation the baby was fed on breast-milk. I intended to have the infant fed on the same mixture of cows' milk that was given during the second observation, but concluded not to do so, because he previously had shown a lack of tolerance for cows' milk, and I wished to test his absorptive powers for cows' milk under the most favorable conditions. A comparison of the second and third observations shows that the results were almost identical, so that the interval of breast-milk feeding did not appear to exert any marked influence on the second observation. I did not wish to test the tolerance of the infant for cows'-milk fat, but, on the other hand, I desired him to ingest, if possible, an amount of fat compatible with a gain in weight. In addition to this, it was desirable for purposes of comparison that approximately the same quantity of fat should be ingested in each observation, and it was improbable that the breast-milk would contain much less than 3 per cent. of fat.

At the hour selected to begin the first observation a Babcock test of the breast-milk showed 5.4 per cent. of fat. As the supply of breast-milk was limited I had the alternative of postponing the observations, with a very good chance that something else would occur to complicate matters, or of using this milk for the first twenty-four hours and securing milk from another wet-nurse for the remaining forty-eight hours. Under the circumstances it seemed wiser not to postpone the observation.

At the end of the first twenty-four hours the infant was not so hungry as usual and left some of the milk. On the next day the milk was obtained from another wet-nurse and contained 2.5 per cent. of fat. The baby's appetite returned and he showed no further signs of disturbance. The excessive quantity of fat taken the first day may have influenced the subsequent absorption of fat. The weight of dried feces during the breast-milk period very much exceeded that of either of the other two periods. There is always an unknown and unavoidable error in the segregation of feces, but the difference between these periods appears to me to be larger than can be accounted for on this ground.

#### CONSIDERATION OF RESULTS

The dried feces from the breast-milk period contained 33.4 per cent. of fat; from the first cows'-milk period 54.4 per cent. and from the second cows'-milk period 52.75 per cent. This difference between the breast and cows'-milk periods is offset to a great extent when the total percentage of excreted fat is estimated. If we assume that the fat in the feces represents fat that has been ingested, then 10.6 per cent. of the ingested fat was excreted in the feces during the breast-milk period against 11.5 per cent. during each of the cows'-milk periods. I have little doubt that the absorption of fat during the breast-milk period was disturbed by the excessive quantity of fat ingested the first day, and that these percentages do not afford an accurate basis for comparison of the three periods. If we consider the actual quantity of fat ingested and absorbed in each of the three periods an entirely different result is obtained. During the breast-milk period the infant ingested 11 gm. and absorbed 10.35 gm. more fat than during either of the cows'-milk periods. In other words, he absorbed 16 per cent. more fat during the breast-milk period than during either of the cows'-milk periods. It may be argued that, if the cows'-milk fat had been raised to 5.4 per cent. for one day, as was the case with the breast-milk, then the absorption of fat in the cows'-milk periods would have equaled that in the breast-milk period. This did not prove true in a patient with infantile atrophy fed on a cows'-milk mixture in which the fat was increased from 2.5 to 3 per cent., the other ingredients and the

daily quantity remaining unchanged. When the milk contained 2.5 per cent. of fat the dried feces contained 41 per cent.; when the milk-fat was raised to 3 per cent. the dried feces contained 50.5 per cent. of fat. This was a marked increase in the excretion of fat following a relatively slight increase in the fat ingested. Such a high percentage of cows'-milk fat as 5.4 if given to this atrophic infant, who had previously shown his inability to tolerate 3 per cent., would, in my opinion, have terminated the metabolism observation on the first day, owing to the disturbance which it would have caused in the digestion.

The apparent intolerance for cows'-milk fat previously shown by this infant, the fact that so little digestive disturbance followed the administration of an excessive quantity of human milk-fat, and the much larger quantity of fat absorbed during the breast-milk period, may safely be accepted as evidence of a much greater tolerance for human milk fat than for cows'-milk fat. Whether this difference is due to difference in the two kinds of fat or to the presence or absence of other ingredients in the two kinds of milk can be determined only by further experiments.

It is interesting to note that only 4 or 5 per cent. of the fat in the feces is present as neutral fat. I have recently confirmed this observation in a number of normal and atrophic infants. The rennet preparation of cows' milk did not appear to favor the absorption of fat as compared with a similar mixture of cows' milk without rennet.

#### COMPARISON OF WEIGHTS

A comparison of the weights of the infant during the three metabolism periods cannot be made, because the caloric value of the breast-milk and cows'-milk mixtures was not identical. It is interesting, however, to note the gain in weight that was coincident with the administration of breast-milk, which persisted as long as sufficient quantities of breast-milk were given, and that the tolerance for cow's milk became much improved during this time.

The baby was under observation for twenty days previous to admission to the Massachusetts Infants' Asylum. He was 13½ weeks old and presented the usual symptoms of infantile atrophy. A tuberculin skin test was negative. For the first three days of this period he was given a whey-and-cream mixture which contained 3 per cent. of fat, and for the following nine days a similar mixture which contained 2.5 per cent. of fat. The food was then changed to a mixture of cow's milk which contained from 2.75 to 3 per cent. of fat, 6 to 6.5 per cent. of milk-sugar and 1 to 1.5 per cent. of protein. The daily quantity was 840 c.c. There was very little change in the weight during these twenty days—at the beginning

3,460 gm. and at the end 3,450 gm. The food was not well digested at any time and the baby vomited occasionally.

He entered the Massachusetts Infants' Asylum February 18, at the age of 17 weeks, and was given a mixture of cows' milk for one day and a malt soup mixture for two days. His condition was so bad at this time that he was given breast-milk. From this date (February 21) to March 10 he was fed on breast-milk and gained in weight from 3,430 to 3,890 gm. in seventeen days; that is, a gain of 460 gm. The daily quantity of breast-milk ranged between 840 and 890 gm. (28 to 29½ ounces).

Beginning March 10 he was given daily 840 c.c. of a modification of cow's milk which contained approximately 3 per cent. of fat, 6 per cent. of milk-sugar and 1 per cent. of protein. This was continued until March 21. The weight March 10 was 3,890 gm., and March 20 it was 3,950 gm., a gain of 60 gm. in eleven days.

Vomiting occurred on March 21 and for a time the baby was given alternate feedings of breast-milk and a whey-and-cream mixture. March 23 his weight was 3,880 gm., and from this date until April 8 (eighteen days) the whey-and-cream mixture and breast-milk were continued in the proportion of one-third to one-half breast-milk. An uninterrupted gain in weight occurred from 3,880 gm. to 4,260 gm.—380 gm.

From April 8 to April 28 a modification of cow's milk containing approximately 3 per cent. of fat, 6 per cent. of milk sugar, and 1 per cent. of protein was substituted for the whey-and-cream-mixture and alternated with breast-milk. The baby continued to gain weight from 4,260 gm. to 4,780 gm.—520 gm. in twenty days. During the period from March 23 to April 28 the daily quantity of food varied between 925 and 1,000 c.c. April 28 he was 26½ weeks old and tolerated 3 per cent. of cow's-milk fat in from one-half to two-thirds of the daily quantity of food ingested. At this time the breast-milk was omitted and he was given 960 c.c. daily of a whey-and-cream mixture. At the end of nine days the modification of cow's milk that previously had been tried was substituted for the whey-and-cream mixture and the baby was put out to board. During these nine days he gained only 80 gm. His tolerance for cow's-milk had improved so much that he was able to continue to take mixtures of cow's-milk and was sent home in the following September when he was 11 months old, weighing 6,120 gm.

I am glad of the opportunity to thank Dr. E. C. Stowell for his great kindness in permitting me to carry out this investigation in the wards of the Massachusetts Infants' Asylum.

In addition I wish to thank the superintendent, Miss Cheney, and her assistant, Miss Mabry, for their supervision of the infant during the observations.

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## FURTHER INVESTIGATIONS IN EXPERIMENTAL MYOCARDITIS\*

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A little over a year ago, we found that one single injection of 0.2 c.c. of adrenalin causes, in many cases, the appearance of a myocarditic lesion in rabbits,<sup>1</sup> and that the injection of small doses of spartein (0.012 gm. per kilogram) or caffein (0.025 gm. per kilogram), followed by the injection of a small quantity of adrenalin (0.2 c.c. of a 1 to 1,000 solution), produced macroscopic changes in the hearts of 60 per cent. of the animals and microscopic changes in almost all cases. We concluded therefrom that the typical effect of the intravenous injection of adrenalin was a cardiac, and not an aortic lesion.

### I. MYOCARDITIC LESION PRODUCED BY ONE INJECTION OF ADRENALIN

This method of producing a myocarditic lesion enabled us to study the sequence of the changes which resulted from these injections, by examining the animals at various periods after the single injection. The changes which take place during the first six weeks we have already fully described, and, now, we desire to call attention to the changes noted at periods between six and twenty weeks after the injection.

We published a preliminary report<sup>2</sup> concerning the changes noted in the rabbits' hearts at periods of from six to fifteen weeks after the injection; we shall here describe those changes more fully and, at the same time, review all the experimental work which we have so far carried on regarding myocarditic lesions. Observations concerning the appearance of the myocarditic lesions at periods twenty weeks after the injection are here added. The effects of two injections of spartein and adrenalin will

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\* From the Laboratory of Experimental Pathology, University of Pennsylvania.

1. Fleisher, M. S., and Loeb, Leo: Experimental Myocarditis, *THE ARCHIVES INT. MED.*, 1909, iii, 78.

2. Fleisher, M. S., and Loeb, Leo: The Later Stages of Experimental Myocarditis, *Jour. Am. Med. Assn.*, 1909, liii, 1561.

also be described, as well as various other observations which have been made in the course of the study of these myocarditic lesions. We shall first review in a brief manner the sequence of the changes noted in the first six weeks.

Macroscopically, the lesion may be noted as early as two days after the injection, but it is most marked when seven or more days have elapsed. The most common site of the lesion is the posterior wall of the left ventricle, close to the base and near the posterior intraventricular sulcus. The lesions vary considerably in size, but never affect the whole of the left ventricle. The apex is usually not involved, but the papillary muscles frequently are. The diseased area is pale and of a yellow brown color, as contrasted with the red brown of the normal cardiac tissue; it is stiffened and has lost its pliability and is usually thickened.

Microscopically, the earliest change noted is separation of the muscle-fibers, and this may be found even a few minutes after the injection. Two days later, the muscle-fibers may be separated, and swollen, and the cross-striations seem to be a trifle paler than normally. Not only are the muscle-fibers increased in size, but the nuclei, also, are larger. Even at this early period, the number of young connective tissue cells between the muscle-fibers is increased.

In the next few days the changes become more pronounced. The separation of the muscle-fibers which is probably due to edema, is marked. In places, degenerative changes in the muscle fibers may be noted; some fibers appear to have been dissolved, leaving only a thin ring of muscle substance surrounding the nucleus; in other places, the fibers are hypertrophied, and at other places, they contain vacuoles of various sizes.

At the period between twelve and twenty-one days after the injection, the changes have reached their maximum. The increase of connective tissue is now diffuse, especially marked around the blood-vessels and around the endocardium and pericardium, but it is also present between the muscle-fibers. The degenerative changes have also progressed; there are small areas in which the muscle-fibers are more or less dissolved and, throughout the fibrillar connective tissue network which is left, are scattered the nuclei of the muscle-fibers, surrounded by a pale ring of muscle substance. Most of the muscle-fibers are increased in size, although, occasionally, an atrophic fiber is noted, showing an increase of the perinuclear pigment. The transverse striations have become less clear but are not completely destroyed. Vacuoles within the cells are more frequent, but can by no means be said to be common; they appear usually in the cells near the endocardium, but are not confined exclusively to this portion of

the heart. The nuclei are larger than usual and the appearance of double nuclei within the cells is more frequent.

Microscopically, we find that the interstitial changes begin soon after the injection and become steadily more marked; in the early periods, they are only noticeable around the blood-vessels, endocardium and pericardium; later, all the connective tissue elements take part in the proliferation. In the parenchyma the principal and earliest change noticeable is an increase in size of the muscle-fibers and, associated with this, is an increase in size of the nuclei and increase in the number of the double nuclei.

We have noted the changes in the connective tissue very shortly after the injection, and usually at a time when no marked degenerative changes were noted in the muscle-fibers. Thus, at a period twenty-four hours after the injection, there was separation of the muscle-fibers, that is, edema of the supporting tissue, and forty-eight hours after the injection, we have noted an increase of the young connective tissue cells. At this time the only change noted in the muscle-fibers was an increase in size, due probably to edema, and, in the sections examined, we found no marked degenerative changes in the muscle-fibers, such as paling of the cross-striations and vacuolization, until the third or fifth day. We do not necessarily conclude from these results that the connective tissue changes always appear earlier than the degenerative changes, for there may be some cases in which the degenerative changes appear at an earlier stage than we have noted them. Whether the proliferative connective tissue changes are primary, or whether they are secondary to changes in the muscle-fibers (edema of the muscle fibers), we cannot state with certainty, but it would seem that the early interstitial changes are in many cases not secondary to the parenchymatous changes, but result from the edema which is noted very shortly after the injection. Therefore, it is probable that the early interstitial and parenchymatous changes are usually independent of one another, and that they are due to one and the same causal factor.

We have already called attention to the fact that the lesions produced by the injection of spartein or caffein and adrenalin are essentially the same as lesions noted in hearts of animals in which cardiac hypertrophy had been produced experimentally, or in cases of hypertrophy of the human heart as found at autopsy.

Altogether, we have examined the hearts of one hundred and twenty rabbits killed at various periods within the first six weeks after the injection of spartein and adrenalin, and we have found gross myocarditic lesions in 63 per cent. Forty-six rabbits have been examined at various periods later than six weeks after the injection and only 22 per

cent. showed macroscopical myocarditic lesions. These were examined eight, ten, fifteen, and twenty weeks after the injection. Myocarditic lesions were found in between 22 per cent. and 27 per cent. of the rabbits examined at eight, ten, and fifteen weeks, but in only 15 per cent. of those examined after twenty weeks.

When a myocarditic lesion is present at ten to twenty weeks after the injection, it is usually smaller, and shades more gradually into the normal tissue than those noted at earlier periods. The loss of pliability of the ventricular wall is still noticeable, but only rarely is the wall thickened. In short, the lesion appears to be retrogressing.

On microscopical examination, changes are noted even in those hearts which show no lesion macroscopically. But even the microscopical lesions are much less marked at eight weeks than those at the earlier periods. The hypertrophy of the muscle-fibers is less marked, and fewer double nuclei are noted. The connective tissue increase is still diffuse and, in a few places, there appear areas of connective tissue replacing degenerated muscle-fibers. Most of the degenerative changes have disappeared and it is only rarely that vacuolization of the muscle-fibers is found.

At periods from ten to fifteen weeks after the injection, the hypertrophy of the muscle-fibers has all but disappeared, and the number of double nuclei is no longer increased. Neither vacuolization of the muscle-fibers nor paling of the cross-striation is noted at this period. The connective tissue has now begun to become fibrous. In some areas there appear tracts of rather dense fibrous tissue containing what appear to be the remnants of degenerated muscle-fibers. In other areas infiltrations with small cells may be seen. The fibrous areas are not diffuse, but are scattered, here and there, throughout the heart. Such areas are usually small, but a few fairly extensive areas are occasionally seen in the central portion of the ventricular wall, or near the endocardium, and occasionally in the papillary muscles.

In the hearts examined twenty weeks after the injection, the conditions are very similar to those just described. However, no degenerative or hypertrophic changes are visible. The increase of connective tissue is the only abnormal feature. At all places the new connective tissue is becoming fibrous. In the central portions of the heart wall, small areas of fibrous tissue separating the muscle-fibers are noted; at other places, most commonly near the endocardium and at the base of or in the papillary muscles, areas of connective tissue seem to have replaced the degenerated muscle-fibers; these areas are usually small. In other places small connective tissue cells are scattered between the muscle-fibers. In some hearts these changes are quite extreme, in others almost no changes are



noted; in only one of the eleven hearts examined microscopically twenty weeks after the injection, could no changes whatever be seen. On the whole, the connective tissue appears to be slightly less at this period than in hearts examined ten or fifteen weeks after the injection.

At twenty weeks the connective tissue is, therefore, more fibrous, but is not so extensive nor is it so diffuse as it was at earlier periods.

At a period six weeks after the injection of spartein and adrenalin, practically all of the preexisting connective tissue shows activity and, throughout the ventricular wall, between the muscle-fibers, about the vessels and near the endocardium, the number of young connective tissue cells is increased. Eight, ten, or fifteen weeks after the injection, the connective tissue increase is less diffuse and has become confined to small areas in the central portion of the ventricular wall, or in the base of the papillary muscles or in the papillary muscles themselves. Furthermore, the connective tissue is becoming fibrous. At a period twenty weeks after the injection, we find only a few scattered areas of fibrous tissue which, in most cases, appear to be replacing atrophic or degenerated muscle-fibers. These areas of connective tissue are smaller than those noted at eight, ten, or fifteen weeks and, on the whole, there is less connective tissue present twenty weeks after the injection, than six weeks after the injection.

The interstitial changes appear to have reached their maximum about six weeks after the injection and, from this time onward, the connective tissue changes grow less marked, until the only signs of the connective tissue overgrowth are the fibrous areas replacing the degenerated muscle-fibers. Thus, the only places in which the increased connective tissue persists are those where its increase has been secondary to the degenerative changes. It is of considerable interest to observe that an actual connective tissue increase may apparently disappear entirely in certain parts of the heart wall. We expect, however, to extend our investigations into the ultimate fate of the connective tissue, and we do not regard our conclusions as final, as far as the diminution in the amount of connective tissue is concerned.

It is also of interest to note that twenty weeks after the injection, all degenerative changes have disappeared and in only a few small areas do we find evidence that connective tissue has replaced the degenerated muscle-fibers. In an effort to determine whether any regenerative changes could be noted in the muscle-fibers, we have examined the apex and septum as well as the site of the lesions, but we found no evidences of regeneration or compensatory hypertrophy; it is, therefore, probable that the less pronounced degenerative changes in the muscle-fibers rarely lead to the

actual destruction of the muscle-fibers and that a recovery of the muscle-fibers may take place in many cases.

Thus, in spite of the rather severe changes noted in both the parenchyma and the interstitial tissue of the heart at a period shortly after the injection of spartein and adrenalin, we find that in a relatively short time, these changes disappear and only very slight evidence is left of the earlier presence of any pathological condition. It appears that the myocarditic lesion actually heals and that in many cases the repair is not due to the replacement of the injured parenchyma by fibrous tissue, but by a recovery of certain muscle-cells.

## II. EFFECT OF SECOND INJECTION OF ADRENALIN

Thus far, we have spoken only of the influence of a single injection of spartein and adrenalin. It was of interest to determine in what manner a second injection of spartein and adrenalin influenced the frequency and the severity of the myocarditic lesions.

We find that, when rabbits are injected with spartein and adrenalin on two successive days, 54 per cent. of them show gross myocarditic lesions two weeks after the last injection. When the two injections are separated by a period of two weeks, 53 per cent. of the rabbits develop lesions. In none of these cases are the lesions more extensive than after one injection, and the microscopic changes are also similar to those noted after a single injection. When a period of nine weeks elapses between the first and second injection 83 per cent. of the animals show myocarditic lesions; 25 per cent., however, show retrogressing lesions, while only 58 per cent. show fresh lesions.

It appears, therefore, that the first injection is of the greatest importance in causing the appearance of the lesion and that the giving of two successive injections does not increase the occurrence of the lesions provided the second injection be given before the lesions are fully developed or at the time of their full development. If, however, the second injection is given at a time when the lesions have begun to retrogress, the second injection causes the appearance of new myocarditic lesions in the usual percentage of the animals injected, irrespective of whether lesions had or had not resulted from the first injection. No increase in resistance, no immunity has therefore been conferred on animals that have recovered from the effects of a first injection.

## III. EFFECT OF ADRENALIN AND SPARTEIN ON KIDNEYS

In an earlier communication we stated that no renal lesions were noted as a result of the injection of adrenalin and spartein. Since then,

we have carried further our investigation regarding the influence of these injections on the kidneys. We collected the urine secreted by the injected animals, and compared the quantity secreted by these animals in twenty-four hours with the quantity secreted by normal animals. We also made tests for albumin in the urines of the injected animals.

The quantities of urine secreted by the individual rabbits varied considerably, but, in general, no differences were noted between the amounts of urine secreted by normal and injected rabbits. The degrees of the individual variations, as well as the average amounts of urine secreted, were approximately the same in both series.

Among twenty-six injected rabbits, half of which had been injected twice, five showed albuminuria. Two of these five had pneumonia and pleurisy and in these cases the infection probably caused the albuminuria; two others showed but a faint trace of albumin in the urine. It seems hardly probable that the albuminuria in the three cases was due to a renal lesion produced by the injection of spartein and adrenalin, since some apparently normal rabbits also eliminated albumin in their urine. Thus it appears that the injection of spartein and adrenalin does not interfere with the functions of the kidney under otherwise normal conditions.

#### IV. INFLUENCE OF MYOCARDITIC LESIONS ON SECRETION OF URINE

We have likewise tested the influence of these experimental myocarditic lesions on the secretion of urine, the production of peritoneal transudate and the blood-pressure.<sup>3</sup> We found that, in rabbits with myocarditic lesions, the arterial blood-pressure is slightly lower than usual; furthermore, that such rabbits are not as well able to resist the injurious effect of the intravenous infusion of large quantities of 0.85 per cent. sodium chlorid solution as normal rabbits, and that, in rabbits with heart lesions, such an infusion leads to a gradual steady fall of the arterial pressure. Although the amount of peritoneal transudate resulting from such hydremic plethora was not influenced by the presence of a myocarditic lesion, the elimination of the infused fluid through the kidneys was markedly diminished in rabbits with myocarditic lesions. This lessened elimination was probably due to the lowered blood-pressure which resulted from the inability of the diseased heart to respond to the extra strain put on it by the increased bulk of fluid within the vessels.

#### V. INFLUENCE OF MYOCARDITIC LESIONS ON EDEMA OF LUNGS

It has likewise been noted<sup>3</sup> that when animals with myocarditic lesions were infused with large quantities of sodium chlorid solution or sodium-

3. Fleisher, M. S., and Loeb, Leo: *Jour. Exper. Med.*, 1909, xi, 480, 627, 641.

chlorid-calcium-chlorid solution, edema of the lungs appeared more frequently than when normal animals were subjected to similar infusions. It may be that the more frequent occurrence of edema of the lungs in animals with myocarditic lesions is due to the disproportionate amount of work being done by the two ventricles: thus, while the right ventricle discharges a normal or increased amount of blood into the pulmonary arteries (increased because of the hydremic plethora), the diseased left ventricle might be unable to discharge the same amount of blood into the systemic vessels, and, as a consequence, the pulmonary circulation would be overfilled. If this explanation of the sequence of events be correct, the above results would appear to support the mechanical explanation of the occurrence of pulmonary edema.

#### VI. INFLUENCE OF MYOCARDITIC LESIONS ON ASCITES

At the present time, we are carrying out a series of experiments in which we are testing the influence of myocarditic lesions on the production of edema and, especially, ascites in animals poisoned with uranium nitrate. Our results, so far, point to the conclusion that the presence of a myocarditic lesion increases the amount of ascitic fluid in animals poisoned with uranium nitrate, in spite of the fact that the secretion of urine is also increased. Our experiments, however, are as yet not sufficiently numerous for us to draw a definite conclusion.

#### VII. INFLUENCE OF SPARTEIN AND ADRENALIN ON PERICARDITIS

In a few of the injected animals we have found pericarditis. Thus, in three different lots of rabbits, including in all forty-two individuals, we have found six rabbits with pericarditis; in no other rabbits, either those injected with spartein and adrenalin (in all about 116 animals) or normal rabbits which were examined in the course of other experimental work, have we found similar conditions. Three of the six rabbits were in the series of animals which were examined twenty weeks after the injection: two showed not only a marked fibrinous pericarditis, but also bilateral pneumonia and fibrinous pleurisy; one of these showed a very slight gross myocarditic lesion while the other showed none. The third animal of this lot which showed pericarditis had no associated pulmonary lesion and no demonstrable gross myocarditic lesion; in this case, the pericardial condition consisted of a rather firm adhesion between the parietal and visceral pericardium over the base of the left ventricle and the lower part of both auricles; the process had, here, evidently healed. In all three of these cases microscopic evidences of myocarditic changes were noted.

In another lot of rabbits that had received two injections separated by an interval of one week, two showed a fibrinous pericarditis at a period fourteen days after the second injection. Both of these animals had also pleurisy and pneumonia and showed marked myocarditic changes to the naked eye.

In a third lot of rabbits which received only one injection of spartein and adrenalin (these were rabbits which were to have received a second injection at a period nine weeks after the first one), five weeks after the injection, one animal showed fibrinous pericarditis which was associated with a marked gross myocarditic lesion as well as with pneumonia and pleurisy. One other animal which died at the same time showed both myocarditis, and pneumonia and pleurisy, but no pericarditis.

The pericarditic condition noted in the above-mentioned cases was as a rule not localized over the left ventricle, but the fibrin deposit appeared on all parts of both ventricles and also on the auricles. In view of the almost constant association of pneumonia and pleurisy with the pericarditis, it appears improbable that the myocarditic lesion was the direct cause of the pericarditis, or that the injection of adrenalin and spartein produced the pericarditic lesion in the same direct way as it did the myocarditis. In some cases the pneumonia and pleurisy may have preceded the pericarditis: it seems, however, very probable that the myocarditic lesion rendered the animal more susceptible to a bacterial infection, which latter was directly responsible for the pericarditis, pleurisy and pneumonia.

The myocarditic lesion probably created a condition favorable to a bacterial infection of the pericardium and by interfering with the pulmonary circulation it may, moreover, have indirectly prepared this soil for a bacterial infection of the lungs.

#### VIII. EXCESSIVE MECHANICAL STRAIN THE CAUSE OF MYOCARDITIC LESIONS

We have already expressed our belief that excessive mechanical strain is the direct cause of these myocarditic lesions. The fact that the seat of the lesion is close to the auriculoventricular junction near the place of insertion of the muscle-fibers of the left ventricle, where naturally the greatest strain would be exerted, as well as the fact that the lesions are confined to the left ventricle, appear to support this view.

Furthermore, it has been shown in this laboratory, by one of us working with Dr. Strickler,<sup>4</sup> that, although the injections of spartein and

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4. Strickler and Fleisher: Jour. Pharm. and Exper. Therap., 1910, ii, No. 1.

adrenalin will generally produce the same symptoms in dogs as in rabbits, such injections do not cause the appearance of myocarditic lesions in dogs whose hearts are relatively stronger than the hearts of rabbits. It is interesting that in rabbits both arterial and myocarditic lesions can be produced by the injection of adrenalin, while in dogs neither of these changes can be produced.

According to our theory, the myocarditic changes are not due to contraction of the coronary vessels and consequent lack of nutrition in the muscle-fibers. The site of the lesion, as mentioned above, as well as the behavior of the coronary vessels,<sup>5</sup> which are not supposed to contract under the influence of adrenalin, speak against such a theory. But we believe that the appearance of the lesion is due to the excessive contraction of the muscle-fibers of the heart. It has been shown that excessive contraction of striated muscles causes<sup>6</sup> these to take up more fluid, and, after the injection of adrenalin and spartein, we have found edema of the heart muscle, a condition analogous to that noted in the striated muscle.

#### CONCLUSIONS

1. The injection of one single dose of spartein or caffein with adrenalin causes the appearance of gross myocarditic lesions in 60 per cent. of the rabbits injected, and the appearance of microscopic lesions in the hearts of almost all the rabbits.

2. The lesions appear a few days after the injection. The earliest change (separation of the muscle-fibers due to edema) may be noted a few hours after the injection. The gross lesion may become apparent a few days after the injection.

3. The lesions consist in their earlier stages (up to a period of six weeks after the injection) in a combination of the following changes: (a) increase of connective tissue which appears very early and is quite diffuse; (b) hypertrophy of the muscle-fibers, with increase of the double nuclei of the muscle cells and indistinctness of the cross-striation, the first of these appearing approximately as soon as the interstitial tissue changes; (c) marked degenerative processes affecting the muscle-fibers, which are most marked at the later period of this stage of the disease and which seem to appear later than the interstitial and hypertrophic (edematous) changes. It seems probable that the interstitial and parenchymatous changes develop independently of each other, at least at first. At

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5. Langendorff: *Ztschr. f. Physiol.*, 1907, xxi, 551.

6. Ranke: *Tetanus*, Leipsic, 1865. Cooke: *Jour. Physiol.*, 1898, xxiii, 137. Fletcher: *Jour. Physiol.*, 1904, xxx, 414. Loeb, J.: *Arch. f. d. ges. Physiol.*, 1894, lvi, 270.

later stages parenchymatous degeneration induces connective tissue proliferation.

4. At later periods, namely, from eight to twenty weeks after the injection, a gradual disappearance of the changes in the muscle-fibers is observed. The hypertrophy, increased number of double nuclei and indistinctness of the cross-striations gradually disappear. The more marked degenerative changes also disappear and only a few areas remain in which some atrophic muscle-fibers are noted. The connective tissue changes become less marked and less diffuse. Finally, at a period twenty weeks after the injection, the only evidence of the myocarditic lesion noticeable consists in some small fibrous areas which contain the remnants of atrophic muscle-fibers; it is, therefore, certain that these areas of fibrous tissue replace degenerated muscle-fibers and that the connective tissue increase in these areas has been secondary.

5. The disappearance of the degenerative changes in the muscle-fibers does not seem to be due to an ingrowth of muscle-fibers from the surrounding normal tissue into the degenerated areas, but seems largely to be due to the recovery of those muscle-fibers in which the changes had not been very pronounced; at least, we were not able to recognize any evidence of regenerative processes in the muscle cells.<sup>7</sup>

6. When animals which have received one injection of spartein and adrenalin are given a second injection, we find evidence neither of immunity nor of increased susceptibility to the effects of a second injection. Animals which received two injections, separated by intervals of either twenty-four hours or one week, showed relatively the same number of lesions as animals which received only one injection. Animals which received the second injection nine weeks after the first one—thus, at a time when the lesions were retrogressing—developed myocarditic lesions as a result of the second injection in approximately the usual percentage of cases; in such animals, retrogressing lesions which had resulted from the first injection were noted as well as the fresh lesions due to the second injection. In no case did the myocarditic lesions resulting from two injections differ to any marked extent, either macroscopically or microscopically, from those resulting from one single injection.

7. The hearts which show macroscopic lesions we found to be functionally inferior to normal hearts, inasmuch as they are unable to meet successfully a demand for extra work.

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7. Whether or not the increase in the number of double nuclei in the muscle cells indicates a regenerative process, we can not decide, until we find distinct evidence of a multiplication of the muscle cells.

8. It seems probable that in animals with myocarditic lesions the injection of uranium nitrate and of large quantities of water leads to an increase in the amount of ascitic fluid. Our experiments in these directions are, however, as yet not sufficiently extensive to permit us to draw a definite conclusion.

9. The presence of a myocarditic lesion may favor indirectly the occurrence of a fibrinous pericarditis, pleurisy and pneumonia by preparing the soil for a bacterial infection. The injection of adrenalin and spartein is in all probability not the direct cause of the development of pericarditis.

10. We believe that excessive mechanical strain is the direct cause of the myocarditic lesions. The typical seat of the lesion, at the base of the left ventricle, where the greatest strain is exerted, favors this theory. Furthermore, analogous conditions have been shown to occur in striated muscle in conditions of over exertion. The fact that the injection of spartein and adrenalin into dogs whose hearts are relatively stronger than those of rabbits, does not cause the appearance of myocarditic lesions, adds further support to this theory. These lesions are, in all probability, not due to a lack of nutrition of the muscle-fibers as a result of the contraction of the coronary vessels, inasmuch as it has been shown that adrenalin does not cause a contraction of the coronary vessels.

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# THE EFFECT OF PERMANENT CONSTRICTION OF THE SPLANCHNIC ARTERIES AND THE ASSOCIATION OF CARDIAC HYPERTROPHY WITH ARTERIO- SCLEROSIS\*

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The importance of arteriosclerosis as a cause of cardiac hypertrophy is a problem which for many years has attracted the attention of both pathologists and clinicians, but even after the most extensive studies on the subject one must admit that the question is, as yet, far from settled. The great obstacle to the elucidation of this problem has been the difficulty in obtaining an exact method for study. So far, most of our conclusions have been drawn from the examination of autopsy material and it is well known how many and what complicated factors confront one under these circumstances. Diseases of the blood-vessels are so frequently associated with other conditions, such as chronic nephritis, which of themselves may lead to hypertrophy, that it is with the greatest difficulty that one can make accurate deductions concerning the direct influence of arteriosclerosis.

It seems, however, to have been shown satisfactorily that sclerosis of the peripheral vessels is not necessarily accompanied either by an increase in blood-pressure or hypertrophy of the heart. On the other hand, it has been quite generally assumed, since the publication of the work of Hasenfeld<sup>1</sup> and Hirsch<sup>2</sup> that arteriosclerosis of the thoracic and abdominal aorta, and especially narrowing of the lumina of the splanchnic arteries, may be a potent factor in the causation of cardiac hypertrophy. Though Marchand<sup>3</sup> states that he could not, from his own experience, confirm this view, it may nevertheless be said that the careful observations, especially of Hasenfeld and Hirsch, have done much to substantiate this claim.

But the question has not been put to experimental test. It was, therefore, the object of the present study to attempt: first, to reproduce as nearly as possible by experimental methods a narrowing by arteriosclerotic processes of the lumen of the celiac axis and superior mesenteric artery;

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\*From the Department of Applied Medicine, University of Pennsylvania.

1. Hasenfeld: *Deutsch. Arch. f. klin. Med.*, 1897, lxx, 193.

2. Hirsch: *Deutsch. Arch. f. klin. Med.*, 1899, lxxiv, 579.

3. Marchand: *Verhandl. d. Cong. f. Uni. Med.*, 1904, xxi, 60.

and, secondly, to study subsequently the effect of this operation on the blood-pressure and heart. In some previous experiments it was found that constriction of either the superior mesenteric artery or celiac axis in dogs caused an immediate rise in blood-pressure of from 8 to 22 mm. of Hg with an average of 14 mm. Hg; while constriction of the two arteries at the same time about doubled this rise. The rise in general blood-pressure was moreover not fleeting, but persisted in some experiments for at least an hour.

It was thought, therefore, quite possible that permanent constriction of these arteries might be accompanied by a continuous increase in blood-pressure with the development of cardiac hypertrophy.

For the following experiments dogs were used exclusively. The animals were etherized and the abdomen opened to the right or left of the mid-line, sometimes directly in the mid-line. The superior mesenteric artery and celiac axis were dissected free from the dense plexus of nerves which surrounds them as they branch from the aorta, and, by means of the ingeniously devised instrument described by Halsted,<sup>4</sup> aluminum bands 3 to 4 mm. in width were rolled about the vessels. These bands were then tightened about the arteries with the finger until the pulsation in the distal side was greatly reduced in force, or almost obliterated. The wound was then closed.

At intervals covering months after the operation, the blood-pressure of the dogs was studied. For this purpose the cuff devised by Janeway<sup>5</sup> was employed attached to a Stanton manometer. Owing to the fact that the proper apparatus was at first not obtained, and to the fact that some time was required to develop our technic, the blood-pressure of the dogs during the early experiments was not estimated before the operation. Later, however, estimations were made before the operation, often several times, as controls for the later readings.

Bands were thus placed either about the superior mesenteric artery alone, or both the superior mesenteric artery and celiac axis of sixteen dogs. Seven of these dogs died within a week of the operation, two from pneumonia and five from infarction of the intestines following thrombosis of one or both of the constricted arteries. One dog died on the eleventh day of a phlegmon of the stomach and one on the thirteenth day of pneumonia. Several dogs have been studied over a period of from three

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4. Halsted: *Jour. Exper. Med.*, 1909, xi, 373. The band rollers and aluminum were kindly loaned by Dr. Halsted.

5. Janeway: *Proc. Soc. Exper. Biol. and Med.*, 1909, vi, 108.

to five months. In four dogs the superior mesenteric artery alone was constricted; in five dogs both vessels were surrounded by bands. The following is an abstract of the protocols of the last nine dogs.

Dog 279.—Fox terrier type, male; weight 24 pounds.

November 9, 1909: Operation, band placed about superior mesenteric artery; fair pulse in arteries of omentum. Dog recovered well; lost weight.

November 29: Weight 23 pounds; thin, but eating well.

December 7: Weight 23 pounds. Stools hard and black.

December 29: Weight 22½ pounds.

January 12, 1910: Weight 21½ pounds.

January 17: Systolic pressure 130 to 118.

January 20: Weight 23½ pounds.

January 31: Systolic pressure 125 to 112.

February 3: Weight 25 pounds.

April 15: Systolic pressure 135 to 118.

April 22: Systolic pressure 115 to 130.

April 25: Dog killed. Band closely approximated about artery, but lumen patent, though tightly constricted. All the organs are normal.

Dog 280.—Fox-terrier type, male; weight 18 pounds.

November 17: Aluminum band placed about superior mesenteric artery.

November 29: Dog thin; stitch abscess.

December 1: Weight 17 pounds; eats well.

December 10: Weight 18 pounds; in good condition.

January 12: Weight 19 pounds.

January 17: Systolic pressure 100 to 125.

February 3: Weight 18½ pounds.

April: Dog lost.

Dog 276.—Male; weight 18 pounds.

October 26: Operation; band placed about superior mesenteric artery.

November 4: Dog not well; wound healed; languid.

November 8: During last few days stools dark brown and soft; losing weight. Dog died November 8 of pneumonia with purulent pleurisy, congestion of intestines and liver; the band is in place and shows tight constriction of vessel which is patent.

Dog 282.—Black and tan, male.

November 22, 1909: Aluminum band placed about superior mesenteric artery.

November 29: Dog doing well.

December 1: Weight 22 pounds.

December 7: Weight 20 pounds; stools seem normal.

December 15: Systolic pressure 85; weight 22 pounds.

January 12, 1910: Dog in good condition; weight 21 pounds.

January 14: Systolic pressure 70 to 80.

January 26: Systolic pressure 78 to 82.

February 3: Weight 20½ pounds.

April 5: The dog has bad mange; systolic pressure 85 to 100.

April 16: Dog killed. The band is tightly placed about superior mesenteric artery and the vessel is completely converted into a fibrous cord.

Dog 283.—Small white fox-terrier, male; weight 13 pounds.

November 10, 1909: Operation; band placed about superior mesenteric artery.

December 7: Stools soft and dark; weight 11 pounds; does not eat well.

December 15: Improving; weight 10 pounds; stools soft and dark.

January 5, 1910: Weight 12 pounds.

January 12: Weight 14 pounds.

January 26: Systolic pressure 90 to 95.

February 3: Weight 15 pounds.

April 5: Systolic pressure 85 to 100. Dog in rather poor condition.

April 6: Dog killed on account of mange. The superior mesenteric artery is converted into a fibrous cord and completely occluded. The organs are normal. Berlin blue injected into the femoral artery reaches the entire small intestine before it colors the stomach.

Dog 208.—Brindle, male.

December 7, 1909: Operation; aluminum bands placed about superior mesenteric artery and celiac axis; marked thrill on distal side of bands.

December 8: Systolic pressure 95 to 105.

December 10: Good condition; stools lost; weight 28 pounds.

December 15: Weight 27 pounds; systolic pressure 120 to 125; there is a diarrhea.

December 29: Systolic pressure 85.

January 5, 1910: Weight 27 pounds.

January 12: Weight 26 pounds; condition good.

January 14: Systolic pressure 95 to 102.

January 22: Stools again normal.

January 26: Systolic pressure 95 to 100.

February 3: Weight 27 pounds.

April 5: Dog is thin and has the mange; systolic pressure 105 to 110.

April 18: Dog killed. Both bands in place and both arteries patulous, though the lumina are constricted.

Dog 290.—Large black and white, male; weight 36 pounds.

December 15, 1909: Systolic pressure 115 to 120.

December 17: Systolic pressure 113 to 120.

December 18: Systolic pressure during operation 107 to 115. Operation, bands placed about superior mesenteric artery and celiac axis; immediately after bands in place systolic pressure 115 to 125.

December 20: Dog in good condition; pressure cannot be obtained.

January 5, 1910: Weight 32 pounds.

January 14: Systolic pressure 128 to 132.

January 20: Weight 34 pounds.

January 26: Systolic pressure 128 to 132.

February 3: Weight 35 pounds.

February 15: Systolic pressure 128 to 130. Soft brown stools.

March 14. Dog killed. The celiac axis is completely converted into a fibrous cord; the superior mesenteric artery is surrounded by the band; the lumen is narrowed to almost pin-hole size, but patulous; the organs are normal.

Dog 293.—Brown, fairly large male; weight 26 pounds.

January 10: Systolic pressure 90 to 93.

January 11: Systolic pressure 92 to 87. Operation, bands placed quite tightly about superior mesenteric artery and celiac axis; scarcely any pulsation felt in distal part of artery.

January 12: Dog in good condition; systolic pressure 74 to 77.

January 17: Systolic pressure 110 to 112.

January 20: Weight 20 pounds.

January 21: Dog developed bloody stools, vomited blood and died.

The stomach shows hemorrhagic phlegmon; the intestines are intensely congested; the bands surround the celiac axis and superior mesenteric artery and seemingly constrict the lumen, but do not occlude it.

Dog 294.—White pointer, large male; weight 30 pounds.  
 January 10: Systolic pressure 92 to 107.  
 January 17: Systolic pressure 98 to 112.  
 January 18: Operation, bands put about celiac axis and superior mesenteric artery.  
 January 20: Dog in good condition; weight 30 pounds.  
 January 24: Systolic pressure 111 to 124; wound not healing well.  
 January 31: Wound in much better condition; systolic pressure 115 to 130; weight 24½ pounds.  
 February 7: Systolic pressure 90 to 100.  
 April 15: Systolic pressure 120.  
 April 22: Systolic pressure 120 to 110.  
 April 27: Dog killed. The organs are normal except for some congestion of the liver. The superior mesenteric artery and celiac axis are tightly surrounded by the bands, and the lumina are constricted to pin-hole size, but patulous.

Immediately after the operation all the dogs rapidly lost weight, but in many instances this was soon regained. Digestive disturbances were frequent. A few dogs developed diarrhea with soft dark stools; one dog died with extensive phlegmonous gastritis.

The effect of constricting the superior mesenteric artery and celiac axis may be seen in Table 1.

TABLE 1.—EFFECT OF CONSTRICTION OF SPLANCHNIC ARTERIES ON BLOOD-PRESSURE \*

No	Operation Date	Arteries Constricted.	December 13	December 15	December 17	December 18	December 20	January 10	January 11	January 14	January 17	January 18	January 24	January 26	January 31	February 7	February 10	February 16	February 21	April 5	April 15	April 22	Death, Date.
279	11/9	Sup. mesent.....			123										111						124	121	4/23
280	11/17	Sup. mesent.....									113												Lost
282	11/22	Sup. mesent.....							76					81					97				4/16
283	11/30	Sup. mesent.....												91					90				4/6
288	12/7	Sup. mesent. and celiac axis.	100	122		85		68						97					102				4/16
290	12/18	Sup. mesent. and celiac axis		117		119		130						129		129							3/14
293	1/11	Sup. mesent. and celiac axis.						92	92		112												1/21
294	1/18	Sup. mesent. and celiac axis.						102	105				117		124	95				120	115		4/27
295	2/13	Sup. mesent. and celiac axis.									116		102		119		98		102				2/23

\* The numbers are the averages of 6 to 12 separate readings. The systolic pressure is computed from the moment that the pulse in the paw disappears.

It is evident that there is no definite change in the blood-pressure following these experiments. In Dogs 290, 293, and 294 there is a slight rise varying from 11 to 19 mm. Hg after the operation, but the elevation

is not constant and is not sustained. In no instance did the blood-pressure rise above a limit which is reached by normal dogs, as could be determined in control experiments. Except for the transient disturbances described, no ill effects on the health of the dogs could be observed.

After periods varying from four to six months the dogs were killed and their hearts weighed by Müller's<sup>6</sup> method. Table 2 gives the results of this analysis, which may be compared with the figures from twenty-eight normal dogs used as controls.

TABLE 2.—RATIO OF BODY WEIGHT TO WEIGHT OF WHOLE HEART AND VENTRICLES IN 28 NORMAL DOGS

No.	Operation.	Duration of Experiment.	Condition at Death.	Weight of Dog in gm.	Whole Heart in gm.	Pro-portion.	Ven- tricles in gm.	Pro-portion.
298	Sup. mesent. and celiac axis.	1 day.....	Fair.....	13,610	109.5	.0080	99.5	.0073
297	Sup. mesent. and celiac axis.	7 days.....	Fair.....	7,400	64.0	.00857	56.0	.0075
295	Sup. mesent. and celiac axis.	7 days.....	Fair.....	13,560	122.5	.0090	111.0	.00818
293	Sup. mesent. and celiac axis.	11 days.....	Wasted, lost 6 lbs.	8,400	84.5	.010	77.7	.009
282	Sup. mesent.....	4 mos., 7 days	Emaciated.....	5,520	51.0	.0092	44.1	.00797
290	Sup. mesent. and celiac axis.	3 months.....	Fair.....	14,500	117.5	.0081	104.0	.0071
279	Sup. mesent.....	5 mos., 24 days	Good.....	11,500	85.5	.00743	75.5	.00656
282	Sup. mesent.....	4 mos., 24 days	Fair.....	9,100	65.9	.00724	59.5	.00653
288	Sup. mesent. and celiac axis.	4 mos., 11 days	Fair.....	11,640	82.5	.00709	75.3	.00647
294	Sup. mesent. and celiac axis.	3 mos., 9 days	Good.....	11,000	90.0	.00818	79.9	.00724

The ratio of body weight to weight of whole heart varied from .0063 to .0089.  
The ratio of body weight to weight of ventricles varied from .0055 to .0075.

When the ratios of the weights of the whole heart and of the ventricles to the body weight of these dogs are examined it is immediately seen that, except for three instances, they fall well within the normal limits. The ratio for the whole heart in the operative series varied between 0.00709 and 0.0086 and for the ventricles between 0.00647 and 0.0075. In twenty-eight normal dogs, used as controls, the figures for the whole heart varied between 0.0063 and 0.00898 and for the ventricles between 0.0055 and 0.0075. Two of the three dogs of the operative series died seven and eleven days, respectively, after the operation and the slight increase in the ratio is unquestionably due to the rapid loss in body weight following operation. The third dog which showed the high ratio was killed four months and seven days after operation. During the last week or ten days of his life, however, he had lost weight very rapidly, which, again,

6. Müller: Die Massenverhältnisse des menschlichen Herzens, Hamburg, 1883.

may account for the comparatively high figure. In all the dogs the valves were carefully examined in order to exclude any accidental valvular lesions which might lead to hypertrophy.

Four dogs died within two weeks of the operation. In three of these, though there was no thrombosis of the arteries constricted, a marked congestion of the stomach, intestines, spleen and liver was found. In two cases this may have been due in part to the acute infection of the lungs which was present, but in one dog this factor could be eliminated. In the fourth dog there was thrombosis of both vessels, but there was no actual infarction of the intestines or of the other viscera. From previous observations and from the clinical symptoms which some of these dogs presented during the first week or two after operation (diarrhea with soft, dark bowel movements) we are led to the conclusion that the first effect of diminishing the arterial blood-supply to the intestines and liver by narrowing the lumen of the superior mesenteric artery and celiac axis is not an anemia, but a congestion of the organs supplied by these vessels.

After complete occlusion of these vessels hemorrhagic infarction develops. During this process, the blood arrives in the intestines by way of the slight collateral anastomosis which the superior mesenteric artery makes with the inferior mesenteric. If, however, the occlusion of these vessels is not complete, there is still sufficient pressure in the distal portion of the arteries to prevent complete hemorrhagic necrosis of the intestines, but not enough to maintain a normal circulation. The result is, therefore, an immediate congestion in this region. But an efficient collateral circulation may be very soon established, for in Dog 297 the superior mesenteric artery was found completely thrombosed seven days after the operation, though there was no hemorrhagic necrosis of the intestines.

Autopsies on the seven dogs that were killed over periods of from three to five months after operation showed that in all cases the organs were normal, except perhaps for some congestion of the liver. In two dogs (279 and 288) the bands were found to constrict either the superior mesenteric artery or celiac axis to a considerable degree, though the lumina of both vessels were patent. In two dogs (282 and 283) the superior mesenteric artery was completely converted into a fibrous cord, and in one dog (290) the celiac axis was completely converted into a fibrous cord, while the lumen of the superior mesenteric artery, though patulous, was narrowed to a pin-hole size. An injection of Berlin blue into the femoral artery of one of the dogs in which the superior mesenteric artery was completely thrombosed showed that a free anastomosis had been estab-

lished between the branches of the inferior mesenteric and superior mesenteric arteries. The injecting fluid was seen to fill the vessels of the colon in the region supplied by the inferior mesenteric artery, and to pass through into the vessels of the small intestines, coloring the loops of the intestines blue before the stomach and spleen were injected.

From these experiments we can conclude, therefore, that extreme narrowing of the mouths of the superior mesenteric artery and celiac axis in dogs is soon compensated for by a collateral circulation, so that gradual thrombosis of one or both vessels may take place without serious or obvious detriment to the health of the animal. Neither cardiac hypertrophy nor hypertension follows the narrowing of the mouths of these vessels in dogs.

Certain criticisms might be offered to such conclusions. It is possible that the time elapsing between the operation and the date of death was not sufficiently long to allow for a noticeable increase in the weight of the heart. Friedländer,<sup>7</sup> however, has found that in children and young adults hypertrophy may be noticeable four weeks after the onset of acute scarlatinal nephritis, and there is no reason to suppose that hypertrophy may not occur as rapidly in dogs. Seven of the dogs were watched at least twice this long, without the slightest evidence of hypertrophy. Again, it may be said that the condition of the life of these animals after operation was not conducive to hypertrophy, but they were kept under exactly the same conditions as the control dogs and, if the operation itself had had any effect on the general vascular system, a comparison with the control dogs should have demonstrated this.

We may now ask whether it is justifiable to draw conclusions from these experiments as regards cardiac hypertrophy in man. To determine this point, we have examined during the last three years with particular care the condition of the branches of the abdominal aorta at autopsy, and have compared the state of these vessels with the weight of the heart. The hearts, however, have not been weighed by Müller's method, but the condition of the organ has been computed by the usual methods. During this time we have found forty-six cases (Table 3) in which either the heart showed hypertrophy or the mesenteric artery and celiac axis were narrowed, often to an extreme degree by arteriosclerotic processes, pressure from aneurisms or from new growths. Naturally, all cases in which there was a valvular lesion or disease of the pericardium have been excluded.

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7. Friedländer: *Arch. f. Physiol.*, 1881, 168.



TABLE 3.—CARDIAC HYPERTROPHY AND SCLEROSIS OF ABDOMINAL AORTA

CARDIAC HYPERTROPHY, 37 CASES			
Associated with sclerosis of abdominal aorta and narrowing of splanchnic arteries.	Chronic nephritis present....	10	12
	Chronic nephritis absent....	2	
Unassociated with sclerosis of abdominal aorta or narrowing of splanchnic arteries.	Chronic nephritis present....	29	25
	Chronic nephritis absent....	5	
Total .....			37

SCLEROSIS OF ABDOMINAL AORTA AND NARROWING OF SPLANCHNIC ARTERIES,  
21 CASES

Cardiac hypertrophy .....	Chronic nephritis present....	10	12
	Chronic nephritis absent....	2	
No cardiac hypertrophy .....	Chronic nephritis present....	6	9
	Chronic nephritis absent....	3	
Total .....			21

In this series, shown in Table 3, there were thirty-seven cases of definite cardiac hypertrophy. Of these thirty-seven cases twelve, or about 32 per cent., showed extensive sclerosis of the abdominal aorta with narrowing of the mouths of the splanchnic vessels, or definite stenosis of one or both of the arteries themselves.

On the other hand thirty, or 81.3 per cent., were associated with chronic nephritis. Of the twelve cases in which narrowing of the splanchnic vessels occurred in combination with cardiac hypertrophy ten, or over 83.3 per cent., showed chronic nephritis and, in the two cases in which there was no nephritis, the hypertrophy was of very slight grade. Finally, there were nine cases in which narrowing of the superior mesenteric artery and celiac axis occurred in which there was no cardiac hypertrophy demonstrable by the methods employed. In five cases, at least, the lesion of the abdominal aorta and splanchnic vessels was of a most extreme grade. In one instance both vessels were almost occluded by pressure from a new growth; in one instance a dissecting aneurism of the celiac axis narrowed the lumen to a mere slit and in three instances there was extreme sclerosis of the abdominal aorta, with much constriction of the superior mesenteric artery and celiac axis. Indeed, of the twenty-one cases in which the splanchnic vessels were narrowed, only seven were associated with any degree of cardiac hypertrophy and in all seven cases a definite chronic nephritis coexisted.

Our experience at autopsy is therefore in accord with that of Marchand,<sup>3</sup> who could find no definite association between cardiac hypertrophy and sclerosis of the abdominal aorta or splanchnic vessels.

From these experiments and observations at autopsy it would seem highly improbable that any anatomical lesion of the larger vessels, even in the splanchnic area, can produce a marked increase of blood-pressure or

give rise to hypertrophy of the heart. The gradual narrowing of the vessels which occurs in such a process, even when it is wide-spread, is soon compensated for by collateral anastomoses, so that the distribution of the volume of blood in the body is equalized.

That narrowing of the main splanchnic arteries may cause a rise of blood-pressure in any other manner than by shutting off into the general circulation a certain proportion of the volume of blood flowing to the intestines is unlikely from the results of previous experiments on dogs; for it was found that the rise of blood-pressure, following immediately on occlusion of the superior mesenteric artery and celiac axis, was not due to a possible reflex arising from the anemic intestines and causing constriction of the arteries in other parts of the body. On the other hand, the excess of blood thrown into the general circulation by this procedure was not sufficiently compensated for by a dilatation of the vessels of other organs, and the general blood-pressure rose, owing to the rapid increase of blood in the general circulation which was not compensated for.

Mall<sup>8</sup> has explained the rise of pressure which follows constriction of the splanchnic arteries and, indeed, the mesenteric veins as well, following stimulation of the splanchnic nerves, on the same basis. The results of sclerosis of the splanchnic arterioles may be quite different from that of narrowing of the main arteries, but the present investigation is, of course, not concerned with this problem. A study, however, of the condition of the finest branches of the mesenteric artery is now being made in connection with observations on the blood-pressure during life.

#### CONCLUSIONS

We conclude, therefore, that sudden occlusions of the superior mesenteric artery in dogs results in hemorrhagic infarction of the intestines. Permanent constriction of the superior mesenteric artery and celiac axis, as well as gradual occlusion of one or both of these vessels, may be present in dogs for at least five months, without giving rise to a definite and constant elevation of blood-pressure or to hypertrophy of the heart.

At autopsy, no definite association can be found in man between sclerosis of the abdominal aorta and great splanchnic vessels and cardiac hypertrophy.

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8. Mall: Johns Hopkins Ho-sp. Rep., 1896, i. 37, 111.

## AN INDIVIDUAL QUANTITATIVE INDEX TO TUBERCULIN DOSAGE IN TREATMENT\*

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Two years ago in a discussion at the National Association meeting,<sup>1</sup> we called attention to the fact that all the surface cells, at least, of the body were in a condition of sensitiveness to the application of the poison which is known to-day as tuberculin, as evidenced by the different methods of tuberculin test which were before the medical profession—the eye reaction, the skin reaction, the urethral reaction, the nasal reaction, etc. We urged at that time that, if this were the truth, the discussion as to the methods of diagnosis which had been used were rather futile; that the method should be chosen which was the least dangerous, most ready of application and most easily observed and controlled.

A year later we called attention to the necessity of getting away from the qualitative studies of this method of diagnosis, and reducing it to some definite quantitative basis, and offered in an article published<sup>2</sup> in the *Journal of Medical Research*, a definite quantitative plan to be carried out in this test.

We do not wish to be accused of entering at this time into a discussion of the value of the cutaneous reaction in diagnosis. We feel that it is a point of evidence in diagnosis to be put on the same basis as the clinical thermometer, chest examination, afternoon tiredness, clinical history and all other evidence contributory to the clinical picture caused by the tubercle bacillus. It has, however, an especial value in ruling out certain cases as non-tuberculous.

At the present time, we feel that on the definite quantitative plan, such as we have suggested, it is possible to determine the exact response which the body suffering from tuberculosis will make to definite quantities of tuberculin introduced beneath the skin. Here it must be borne in mind that it is just as possible to obtain a constitutional reaction to tuberculin applied by the way of a skin test, as it is when the tuberculin is introduced into the body subcutaneously. The following is an example

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\* A study prepared under the auspices of the Hospital Tuberculosis League of Pittsburg.

1. White, W. C.: Proc. National Assn. for the Study and Prevention of Tuberculosis—Discussion—1908, p. 96.

2. White and Graham: Jour. Med. Research, 1909, xx, 347.

of a fair number of cases which have come under our notice, when the patients have been under the routine hospital supervision of regular temperature registration and personal control, and will serve as a proof of this:

On Oct. 8, 1909, Mr. L. was given a skin test on the left forearm, 0.01 cm. of 100 per cent. O. T. being applied. Within an hour reaction had begun, and in twenty-four the reaction was marked; in forty-eight hours very marked, diminishing somewhat in seventy-two hours, the areola remaining, however, for two weeks. At the point of inoculation there was marked swelling, heat and redness, and very noticeable redness, swelling and tenderness of the lymphatic leading from the site of inoculation as far up as the axilla. For four weeks previous to the skin test the temperature had been normal, except on two or three occasions when it reached 90 F. On October 9 at 12 o'clock the temperature was 100.5; at 4, 101, and at 8, 100.5 F. On October 10, at 12 o'clock it was 99, at 4, 100, and at 8, 99 F. The following day (October 11) the temperature was normal. On October 9 the patient complained of weakness, headache and general malaise. In fact, there was a good deal of prostration. The following day (October 10) he complained of weakness, but the headache was gone and there was only slight general malaise.

A year ago, at the meeting of the Association of American Physicians, we read a paper<sup>3</sup> laying down a law of partition of dosage based on the quantitative basis of skin-cell reaction. We regret that what should have been termed a preliminary note was published hastily as a paper. Certain of the figures given at that time we have since determined to be at fault. At the same time we have proved to our satisfaction that the principle contained in that paper is correct, and we wish now to exhibit the result of a year's work which will give the correct partition doses, based on the determination of the minimal cutaneous reaction to definite quantities of tuberculin.

#### REQUISITES IN APPLICATION OF SKIN TEST

We wish first to call attention to certain requisite points which must be carried out in the application of the skin test. The tuberculin must undoubtedly be a solution of tuberculin poison such as is contained in the Old Tuberculin or in the filtrate. Suspensions of tubercle bacilli such as are contained in the Bazillen-Emulsion and in the T. R. are not permissible. The use of a solution of tuberculin is necessary to render absorption of the poison as easy as possible. Suspensions of bacilli containing, as they do, clumps of comparatively fair size with the poison still in the bacillary body, do not permit of ready absorption by the lymphatics, which is necessary, as will be shown later.

The choice of the site for the application of the preliminary skin test is important. Many factors enter into this choice: first, the thickness

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3. White, Graham and Van Norman: Jour. Med. Research, 1909, xxi, 255.

of the cuticle; second, the number and distribution of lymphatics; third, the readiness with which the patient can keep the part at rest until absorption of the solution has occurred; fourth, the absence of hair follicles. The thickness of the cuticle varies greatly in different parts of the body, and necessitates, as we have frequently shown in our work, a different depth of scarification to produce the requisites for uniform absorption. We have found that the inner side of the forearm has, as a rule, a thin cuticular layer which gives uniform results with approximately the same scarification. The distribution of lymphatics in the above location is also fairly uniform, and the channels of lymphatic drainage fairly straight in their course so that in placing tests below one another it is possible, by shifting the lower test to the right or to the left, to obtain a different draining channel from that which is used in the upper test. In the matter of keeping the part at rest to allow as complete absorption as possible, no part answers so well as the forearm, which is under the patient's control and not under the necessity of being used, and can be kept in a horizontal position more easily than any other part of the body. To fulfil all the conditions outlined, we have chosen the forearm.

Preceding the application of the test, to remove any chances of infection, or fat and scurf that may have gathered on the skin, it is best to wipe off the seat of application with alcohol followed by ether.

The scarification we consider a point of very great importance. The former method, in which we followed Pirquet, was to scarify through the drop of solution. This was found to give various results in the same patient at the same and at different times. In our present method, we scarify the cleansed skin with such force as just to pierce the upper layer of the cuticle and to elicit a punctate spot measuring 2 mm. in diameter, the base of which shows bright pink in color. This pink sometimes may not appear for a second or two after the scarification. It can be made deeper, if necessary, to accomplish the desired result by waiting a few seconds and watching for the pink appearance. It is necessary not to draw the least drop of blood.

Objections have frequently been raised to the use of the Pirquet scarifier, reasons being advanced in favor of needles and lancets with which are made longitudinal slits in the skin of deeper grade than that obtained by the Pirquet scarifier. With none of these, however, can we agree, as it is possible only with the blunt-pointed Pirquet scarifier to obtain a depth and size of scarification which can be readily measured, and which will underlie uniformly the measured drop of fluid which we use in this test.

The color-index in the way indicated here can be followed more accurately than in any other way which we have tried. We have found that only with this color-index can we be sure of having gone the requisite depth at the same and at various times, in the same and in various patients. We formerly gave a definite number of twirls with the Pirquet scarifier, but it was found impossible to control this procedure and get the requisite color in different patients, on account of the difference in toughness and thickness of the cuticle.

After having made the proper scarification, a drop measuring exactly 0.01 c.c. of the tuberculin solution to be used is applied by a throttle pipette exactly over the point of scarification. This is then covered with a vaccine shield, kept in place by two strips of adhesive, and the patient directed to hold the arm in a horizontal position for at least an hour, so as to prevent flowing of the drop. These precautions are necessary, because the essential thing in the tuberculin reaction is the absorption of the poison.

#### PRECAUTIONS IN APPLICATION OF TEST FOR MINIMAL CUTANEOUS REACTION

In the former method of application of this test most of our patients reacted to very much higher percentages of tuberculin than is found with the present method, varying from 1 per cent. to 100 per cent. of pure old tuberculin. The majority of them reacted to 0.01 c.c. of 12.5 per cent. of pure old tuberculin. With the present method, when we are sure that all conditions for ready absorption have been fulfilled, the majority of patients react to 1 per cent.; very few require as high concentration as 25 per cent.; very few of them give a minimal cutaneous reaction to a solution higher than 5 per cent., and many of them react to solutions lower than 1 per cent. A fair number give minimal cutaneous reaction with dilutions as low as 0.1 per cent.

We would call a minimal cutaneous reaction one that gives redness and swelling measuring 4 to 6 mm. in diameter within seventy-two hours. Many will object that this is reducing the cutaneous reaction below the point of usefulness, but the longer we work with the cutaneous reaction, the more convinced we become of its absolute specificity and delicate nature, and the more we feel that it is only when under the above precautions one takes into cognizance this delicacy of reaction that one can reach the usefulness to which this method can be put.

We now usually begin with a solution of 1 per cent. of old tuberculin, because this is the solution to which many of the patients give minimal cutaneous reaction. If 1 per cent. is found to be too high, as it is in a fair number of cases, one can judge by the size of reaction, and choose the

next best solution to try, reducing it to one-half, one-fourth or one-tenth, as indicated by the size of the reaction. If no reaction occurs to 1 per cent. solution, one can go to higher concentrations—2, 3, 4 and 10 per cent., as may be indicated by the reaction to the slowly increasing strength of the solution, letting four days elapse between the applications. If time is a factor in determining the beginning dose of treatment, one can apply two solutions at the same time on the same arm. When time is a factor we frequently use 1 per cent. and 0.25 per cent. for a first test.

Many have objected that one occasionally finds, in obtaining reactions to two solutions of different strengths at the same time, that the area of reaction is greater around the point of application of lesser strength than around the point of application of greater strength. This may be true under certain conditions: first, that the weaker solution is applied at a point more proximal than the application of the stronger solution, and second, that the application of the proximal weaker solution is along the same lymphatic channel as the more distal stronger solution. Under these conditions, as will readily be seen in Figure 1, the lower, stronger solution has drained directly through the lymphatic, which it has definitely reddened, to the point of application of the weaker solution higher up in the same channel, giving a much larger area to the solution above, and then is carried through the lymphatic channel above this, which it has perceptibly reddened in its course. It will also be noticed that while the area of redness is greater around the application of the weaker solution, yet the central ulcerated point is much more definite at the site of the stronger solution.

Figure 2 shows the result of two tests given at the same time in the correct way; that is, the weaker solution distal and the stronger solution proximal. The solutions used in the test shown in Figure 2 were 6.25 per cent. (distal) and 12.5 per cent. (proximal) O. T., and it will be seen that the area of reaction in the proximal is about twice the size of the area of reaction of the distal test with weaker solution. A corresponding result is seen in Figure 3 in which 0.1 per cent. and 0.25 per cent. O. T. were used.

So far as we have been able to find, the question of the importance of the lymphatics and the redness of the lymphatic channels produced by the application of the tuberculin skin test has never before been brought to the attention of the profession.

The next illustration (Fig. 4), which has been taken directly from the arms after the applications of varying strengths of solution, will at once convey the truth of the statement that the lymphatic vessels bear a very striking and important part in this reaction, and will give the proof

of the necessity which is required for allowing for the period of more complete absorption of the poison from the point of application; and we would emphasize again that, when two applications of tuberculin are made at the same time, the greatest care must be exercised not to place them in such a way as to allow drainage from them along the same lymphatic channel. This undoubtedly explains the variations of reaction to different strengths of solution which are found in the published photographs of Pirquet and others.

We feel that the question of lymphatic distribution is a point which must be borne very strictly in mind in treatment with tuberculin, the focal reaction around the tuberculous lesion being a requisite factor in treatment. The dose in treatment may be so given as to drain along the lymphatic into the site of the lesion, and thus obtain the benign influence of focal reaction. This would apply to glands, sinuses, bone lesions and lupus.

We would emphasize also this second point, namely, that, in making two applications at the same time, the precautions must always be observed of placing the weaker solution at a point distal to the stronger solution. We feel that, only under the most pressing necessity should two tests on which a dosage is to be determined ever be given at the same time.

When these precautions are observed in the application of the test to determine the minimal cutaneous reaction, we feel that results directly comparable with our own will be obtained.

We must, however, further indicate certain precautions that are necessary to observe in determining the minimal cutaneous reaction, from certain phenomena which have arisen which evidence the vigor of the body cells of the patient to whom the test is applied. We formerly thought that the vigor of the body cells had much to do with the intensity of reaction, having found certain patients who, though they had a lung lesion on physical examination of a first or second stage Turban, with tubercle bacilli in the sputum, did not react to 100 per cent. Old Tuberculin given repeatedly, but who later reacted to a lower percentage after much improvement in general condition and body weight had taken place. We afterward determined that this depended almost, if not wholly, on the depth of scarification, and when we applied the above-outlined method of deep scarification, being sure to pierce the cuticle, these cases were reduced to a minimal cutaneous reaction of 0.01 c.c. of a varying percentage from 0.1 per cent. to 10 per cent. In fact, so striking has this been in the reaction of patients, when the precaution as to depth of scari-



fication is taken, that we have come to look on the scarification as the most important part of the technic.

It has been urged that a part of the skin which has formerly responded to an application of tuberculin by the signs of redness, tenderness and swelling will not react to a later application of tuberculin within a given period of time. This, however, we have proved to be a fallacy, as the same spot will react again to further applications of the same strength of tuberculin, or a lower strength of tuberculin, within at least two months of the time of the application of the test, as is shown in Figure 5.

A caution must here be added on the point of persistence of the sensitiveness to the same strength of tuberculin application. In the hospital many patients who have received tuberculin regularly for a year or more under the method outlined have not changed in their sensitiveness to tuberculin used as a skin test.

We feel that in the past a grave mistake has been committed in confusing susceptibility to tuberculin with the sensitiveness which is produced by the growth of the tubercle bacilli in the living body. All that can be said at the present time is that sensitiveness of the cells of the body to tuberculin is due to the growth of the tubercle bacilli in the living human body, and we have not yet been able to secure undoubted evidence that any increase of sensitiveness has been aroused in the body, in which the tubercle bacilli have grown, by the use of tuberculin. We shall discuss this point in a later paragraph in this paper, but wish to call attention to it at the present time.

Cases which have formerly been described as being hypersensitive to tuberculin, we feel, can all be explained on the basis of the degree of sensitiveness present in the first instance, as indicated by our cases which react to percentages as low as 0.1 per cent. Almost any of the doses of Old Tuberculin formerly given would have produced some degree of reaction in these patients, but, their sensitiveness having been determined by our method, it is possible to give such minimal doses as to avoid the reaction produced in these cases when treated by the former method of administration. The same argument is applicable to those cases of so-called hypersensitiveness after subcutaneous administration of tuberculin for constitutional reaction in diagnosis.

#### THERAPY OF TUBERCULIN REACTION

In discussing the therapy of tuberculin reaction it is necessary to bear in mind three factors; the cells, the serum, and the tuberculin poison, and the interaction of each of these three factors on the two others of the group. All of these relations we do not pretend to have worked out, but,

as a proof of the influence of the serum it may be well to interject here a note on certain studies which we have carried out in relation to the neutralization power of serum on tuberculin in the cutaneous test.<sup>4</sup> In these studies we found one group of patients in whom the serum added to tuberculin was able to augment the reaction. In studying this group during the past year, we have found that the serum of one patient is able to produce a cutaneous reaction in patients who react to 0.1 per cent. O. T. as is shown in Figure 6. We were able to obtain the reaction in two cases: first, in the patient whose serum was used and whose minimal cutaneous reaction is 0.5 per cent., that is, this patient reacted to his own serum; second, in a patient whose minimal cutaneous reaction is 0.1 per cent. The reaction in this patient is shown in Figure 6.

Just what the bearing of this is and how frequently it occurs, we are not prepared at this time to state, but in this patient it had no relation to tuberculin administration, either for treatment or for skin testing, and the only factor that we were able to determine, which might have a bearing, was that the patient at the time had a mild fever; but in trying the serum of other advanced cases with fever there was no reaction produced even on the skin of those patients who were most acutely sensitive to tuberculin.

TABLE 1.—QUANTITY OF TUBERCULIN (O. T.) USED IN CUTANEOUS TEST OF VON PIRQUET.

Dose in c.c.	Concentration of Solution %	Quantity in mg. of O. T. Applied
0.01	0.1	0.01
0.01	0.25	0.025
0.01	0.5	0.05
0.01	1.	0.1
0.01	5.	0.5
0.01	10.	1.
0.01	20.	2.
0.01	50.	5.
0.01	100.	10.

Having stated these precautions and with these preliminary remarks, we can now take up the question of therapeutic doses of tuberculin which can be given on the minimal cutaneous reaction basis. From the table of quantities of tuberculin contained in the various dilutions of tuberculin (Table 1) it will be seen that the most important point in determining the dose to be given for therapeutics, is the use of 0.01 c.c. of tuberculin in the skin test, which gives a definite quantity of tuberculin on which to base a partition dose in the matter of treatment. As outlined in our former paper, we suggested that there was a definite relation between the

4. White and Graham: *Jour. Med. Research*, 1909, xxi, 261.

quantity of tuberculin which produced a certain amount of reaction on the skin and the amount of tuberculin which, given under the skin, could produce varying grades of reaction from a slight local to a maximum constitutional and focal reaction in the individual.

In the former paper we made the statement that "one-fifteenth of the amount of O. T., which, when applied to the skin by our method, produced the minimal cutaneous reaction, would, when given subcutaneously, produce both local and constitutional reactions; that one-thirtieth of the same amount given subcutaneously would produce local without constitutional reaction. Later work has shown that one-fiftieth of the minimal cutaneous reaction dose will produce neither local nor constitutional reactions when given subcutaneously." These figures, we must now state, were not correct, but this was mainly due to the fallacy of our method in applying the skin test, which we have since corrected, as outlined in the first part of this paper.

The past year's work has determined, however, that the quantity of tuberculin contained in 0.01 c.c. of that definite solution of tuberculin which will produce exactly the minimal cutaneous reaction, which we have arbitrarily called 4 to 6 mm. redness and swelling at the site of application of the test, will produce, when given underneath the skin, an area of redness, tenderness and swelling measuring from 2 to 5 cms. From observation on a very few cases it would seem that, if this dose is increased ten times, it will produce the symptoms of constitutional reaction, and if it be reduced in amount to one-tenth, it will be below the amount which will produce even a local reaction at the site of inoculation. We have, however, not yet been able to verify these last two figures in a sufficient number of cases.

In determining the dose on the skin test, and to show how sensitive is its individual biological basis, and how important are the measurements in millimeters which we have outlined, we would cite an individual case representative of a large class.

Mr. A. reacted to a 5 per cent. solution of O. T. giving an area of redness of 13 by 9 mm. in forty-eight hours. Four days later 3 per cent. was given, causing a reaction of 9 by 8 mm. in forty-eight hours. Five days later 2 per cent. was given, the resulting reaction being 8 by 7 mm. in forty-eight hours. Four days later 1 per cent. was given, the reaction being 7 by 5 mm. in forty-eight hours. Four days later 0.25 per cent. was given. In twenty-four hours there was slight redness of 2 mm. at the point of inoculation, but this had faded in forty-eight and seventy-two hours. Four days later 0.5 per cent was given, the resulting reaction being 4 mm. in forty-eight hours.

It will be seen, therefore, that in order to make this arbitrary law applicable, it is absolutely necessary to obtain that quantity of tuberculin which will produce exactly a minimal cutaneous reaction of 4 to 6 milli-

meters, in order to say that the same quantity introduced under the skin will produce redness of 2 to 5 centimeters.

Much of our original discrepancy came from guessing at the quantity of tuberculin to be given therapeutically on the basis of a result from two solutions.

An example would be as follows: A case would be given 5 per cent. as the initial skin test, the reaction being about 1 cm. Five days later 0.5 per cent. would be given, with no reaction. Formerly we would have guessed the basis to be 3 per cent., whereas, there would likely have been a reaction of 4 or 5 mm. to a 1 per cent. solution.

In determining the minimal cutaneous reaction it is necessary to watch the reaction at the end of twenty-four, forty-eight and seventy-two hours. Oftentimes at the end of twenty-four hours there is an outer ring of faint pinkness around the red reaction. This pink often fades at the end of forty-eight hours, and it must not be taken into account in the measurement of the minimal reaction (central redness). Occasionally the reaction, as has been observed by many other writers, is delayed at least forty-eight hours, and it may be as late as seventy-two, or even later. The redness around the control scarification disappears before forty-eight hours while the redness of reaction persists, often for weeks. Our method of registering the minimal cutaneous reaction can be seen by Table 2.

TABLE 2.—SKIN TESTS

Patient.	Date, March.	Percentage of Tuber- culin.	Result *—			
			In 24 Hours.	In 48 Hours.	In 72 Hours.	
Miss E. . . . .	7 '10	1.	.5x.5?	.5x.5?	.5x.5?	M.C.R.
Miss J. . . . .	7 '10	0.5	.5x.4—	.2	?	M.C.R.
Mr. A. . . . .	7 '10	0.25	.6x.6?	.4x.4—	.4x.4?	M.C.R.
Mrs. B. . . . .	7 '10	0.1	.5x.3?	.6x.4?	.5x.4?	M.C.R.
Mr. C. . . . .	15 '10	1.	.7x.7?	.5x.5—	.5x.5?	} M.C.R.=0.5 %
Mr. C. . . . .	20 '10	0.5	.5x.4+	.4x.4—	.4x.4?	
Mr. C. . . . .	25 '10	0.25	.....	.....	.....	
Mrs. D. . . . .	15/10	2.	1.3x.5+	1.5x.1+	1.0x.8?	} M.C.R.=0.5 %
Mrs. D. . . . .	20 '10	1.	.9x.6+	1.3x.8?	1.0x.7?	
Mrs. D. . . . .	25 '10	0.5	.6x.6?	.4x.4+	.4x.4?	
Mrs. D. . . . .	30 '10	0.25	.....	.....	.....	

\* Figures = diameter (in centimeters) of areola of reaction; ? = very slight redness of areola; ? = slight; ? = moderate; + = marked; M.C.R. = minimal cutaneous reaction.

Having determined the dose of tuberculin which will produce under-  
neath the skin an area of redness and swelling measuring 2 to 5 cm.,



Fig. 1.—Showing the reaction after application of 25 per cent. old tuberculin at the distal point and 6.25 per cent. at the proximal point. The reaction around the application of 6.25 per cent. solution is greater than that around that of 25 per cent. Note the reddened lymphatic.



Fig. 2.—Showing definite quantitative response to solutions of varying strength. The strength of the distal solution is one-half that of the proximal solution, and the response approximately one-half.



Fig. 3.—Similar to Figure 2. It also shows shifting of the distal point of application to the ulnar side to avoid the same lymphatic drainage as that of the proximal solution.

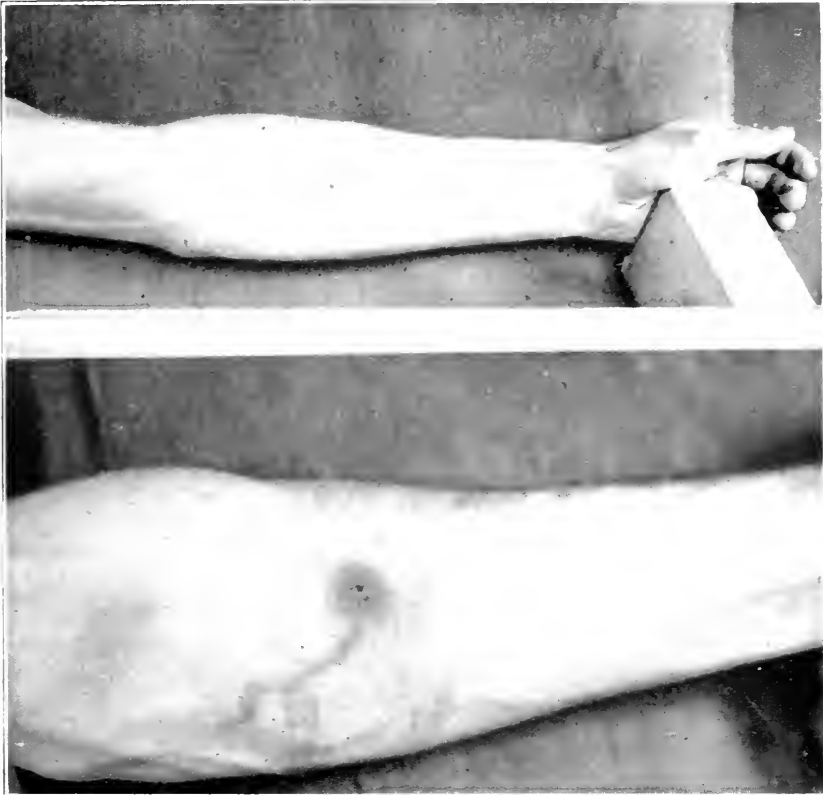


Fig. 4.—Showing reddening of lymphatic leading from point of application of tuberculin.



Fig. 5.—Showing reaction of the application of 1 per cent. old tuberculin to points which previously reacted to 6.25 per cent. and 25 per cent. old tuberculin. These tests were applied to the same spots as shown in Figure 1.



Fig. 6.—Reaction to serum of patient whose serum augmented tuberculin reaction. Notice also lymphatic redness.



which is, as stated above, the quantity of tuberculin which is contained in 0.01 c.c. of the solution of tuberculin which produces a minimal cutaneous reaction measuring 4 to 6 mm., we must next approach the question of what is the desirable therapeutic dose, and the method of procedure for future dosage.

The first question that may fairly be asked is, whether or not we have proof that tuberculin is a valuable therapeutic agent. This can undoubtedly be answered in the affirmative, as everyone who has used tuberculin must have concluded, from its action on bone and gland sinuses, localized tuberculous lesions in glands and various organs (especially would we call attention to certain corneal ulcers), and from its application in lupus. These give, without question, a positive answer to the value of tuberculin in treatment.

The next point to be determined is what dose of tuberculin is the valuable dose. There has been a marked variance of opinion between the German and English investigators in this matter. The German investigators have recently been tending towards the administration of doses large enough to produce constitutional reaction. The English observers have tended towards exceedingly small doses, guided in their therapy by the opsonic index method as indicated by Wright. In this country the English method of small doses has mainly been followed in an outline laid down by Trudeau and Brown, of Saranac Lake. It must have struck most observers who formerly gave tuberculin subcutaneously that patients seemed to improve very markedly in general feeling and in diminution of sputum and often of fever after a constitutional reaction such as was obtained in the former method of diagnostic administration of tuberculin.

Too much importance cannot be laid on Dr. Trudeau's experiments<sup>5</sup> in the tuberculous eyes of rabbits, which were given tuberculin in sufficient doses to produce focal reaction, and which local eye lesions made marked improvement following the reaction. Saathoff<sup>6</sup> has recently called attention to this fact in a paper from Müller's clinic, in which he was able to watch a corneal lesion improve steadily after the repeated focal reactions produced by the tuberculin administration. Dr. Trudeau<sup>7</sup> remarks in a paper published a year ago that "improvement in the lesion may depend on the influence of these mild reactions, but in considering the advisability of utilizing mild, general and focal reactions as a feature

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5. Trudeau, E. L.: *Tr. Assn. Am. Physicians*, May 24, 1892.

6. Saathoff: *München. med. Wchnschr.*, 1909, lvi, 2041.

7. Trudeau, E. L.: *Antibacterial or Antitoxic Immunity in Tuberculin Treatment*, *Jour. Am. Med. Assn.*, 1909, lii, 61.

of treatment, we must not forget that we have no means of controlling the severity of these reactions and that violent reactions are not without danger."

We have been struck with the apparent uselessness of giving small doses of tuberculin in pulmonary and gland tuberculosis, which types of cases mainly have been under our supervision. For two years we followed the method of administration of tuberculin by small doses repeated frequently, and we have at the present time under our care patients who have been receiving tuberculin in this hospital for a period of three years or more. During the first two years of their stay in the hospital they received tuberculin by small, frequently repeated doses, and apparently made no marked improvement other than would be looked for from hygienic conditions. During the past year, however, when they have been treated with doses which produce mild reactions below the fever line, they have made great and noticeable strides, while in the months previous they had been practically at a standstill. It may be objected to this, of course, that tuberculosis takes a wave-like course, but we feel that this is not a valid objection, when the condition has steadily improved with an increased feeling of well-being and diminution of sputum after each local reaction produced by the tuberculin dose. In some of these cases the sputum has diminished to one-half or one-third of the former quantity.

It may be best here, without further discussion, to say that we believe, first, in doses that will produce mild reactions below the fever line in all cases of tuberculosis that admit of tuberculin as a therapeutic agent; second, that the thing to be obtained is the reaction of the cells and not the tolerance to the tuberculin poison. We have come to look arbitrarily on the reaction of greatest good as one which will produce underneath the skin an area of redness, tenderness and swelling of approximately 2 to 5 cm. in diameter at the site of injection. We have not seen a single case to shake our faith in this basis of dosage in the administration of over one thousand injections of tuberculin for therapy, based directly on the minimal cutaneous reaction.

The next point of importance is the spacing of the dosage. We have found that tolerance to tuberculin can readily be established if the doses are given in the Saranac method three or four days apart, and in increasing doses. On the other hand, we have found that, as a rule, when once the dose which will produce the above degree of redness at the site of injection based on the minimal cutaneous reaction has been determined, that patients retain, as a rule, the same degree of reaction for periods reaching as high as nine months. The cases summarized in Tables 3 and 4 illustrate this point:

TABLE 3.—SHOWING UNIFORMITY OF LOCAL REACTION FROM SAME DOSE OF TUBERCULIN \*

Date.	Tuberculin, O. T.	—In 24 Hours—			—In 48 Hours—			Constitutional Symptoms.
		Local Red- ness, cm.	Local Tender- ness,	Local Swelling.	Local Red- ness, cm.	Local Tender- ness,	Local Swelling.	
8 15 09	.0002	2 $\frac{1}{2}$	+	+	3 $\frac{1}{2}$	+	+	—
8 25 09	.0002	2 $\frac{1}{2}$	+	+	5—	—	+	—
9 4 09	.0002	3 $\frac{1}{2}$	+	+	4 $\frac{1}{2}$	+	+	—
9 14 09	.0002	3 $\frac{1}{2}$	+	+	3 $\frac{1}{2}$	+	+	—
9 24 09	.0002	2 $\frac{1}{2}$	+	+	4 $\frac{1}{2}$	+	+	—
10 4 09	.0002	2 $\frac{1}{2}$	+	+	3 $\frac{1}{2}$	+	+	—
10 14 09	.0002	2 $\frac{1}{2}$	+	+	4 $\frac{1}{2}$	+	+	—
10 24 09	.0002	2 $\frac{1}{2}$	+	+	2.5 $\frac{1}{2}$	+	+	—

\* Significance of characters same as in Table 1.

TABLE 4.—SHOWING UNIFORMITY OF LOCAL REACTION FROM SAME DOSE OF TUBERCULIN DURING EIGHT MONTHS \*

Date.	Tuberculin, O. T.	—In 24 Hours—			—In 48 Hours—			Constitutional Symptoms.
		Local Red- ness, cm.	Local Tender- ness,	Local Swelling.	Local Redness cm.	Local Tender- ness,	Local Swelling.	
8 3 09	.0001	2.5 $\frac{1}{2}$	+	+	2.5 $\frac{1}{2}$	+	+	—
8 25 09	.0001	2.5 $\frac{1}{2}$	+	+	2.5 $\frac{1}{2}$	+	+	—
9 27 09	.00015	4 +	+	+	4 —	—	+	—
10 28 09	.0001	2.5 $\frac{1}{2}$	+	+	2.5 $\frac{1}{2}$	+	+	—
11 8 09	.0001	3 $\frac{1}{2}$	+	+	3 $\frac{1}{2}$	+	+	—
11 18 09	.0001	2 $\frac{1}{2}$	+	+	5 $\frac{1}{2}$	+	+	—
11 29 09	.0001	3 $\frac{1}{2}$	+	+	3 $\frac{1}{2}$	+	+	—
1 29 10	.0001	3 $\frac{1}{2}$	—	—	6 $\frac{1}{2}$	+	—	—
2 12 10	.0001	5 $\frac{1}{2}$	—	—	3 $\frac{1}{2}$	—	+	—
2 28 10	.0001	3 $\frac{1}{2}$	+	+	3 $\frac{1}{2}$	—	+	—
3 14 10	.0001	3 $\frac{1}{2}$	+	+	4 $\frac{1}{2}$	+	+	—
4 4 10	.0001	3x2 $\frac{1}{2}$	+	+	5x4—	+	+	—

\* Significance of all characters same as in Table 3.

Consequently, having determined to our own satisfaction that patients do better when they retain their reaction to tuberculin, we feel that it is infinitely better to continue the same dose with an interval of fourteen days between doses. A word of caution must be added here, namely, that a skin test, with the readiness with which tuberculin is absorbed, is equivalent to a therapeutic dose of tuberculin and, if the first dose of tuberculin for therapy be given within a few days after the exhibition of a skin test, the resulting local reaction at the point of injection is apt to be greater than if the injection of the therapeutic dose is delayed fourteen days.

The choice of the site of injection of the therapeutic dose of tuberculin is not apparently a matter of great importance, as we have determined without failure up to the present time that the same dose of tuberculin given in either arm, leg or trunk produces approximately the same degree of redness and tenderness.

A word or two here in reference to the technic of administering tuberculin might not be amiss. We have already mentioned that, whether the tuberculin be given in the legs, arms or trunk, one always gets approximately the same amount of redness and tenderness with the same dosage. As a rule, however, in tuberculin treatment, we begin by using the arms, each arm being used alternately. The tuberculin is administered in the arm between the shoulder and elbow on its posterior aspect, that is, over the triceps muscle. It should be given just under the skin and not injected deeply. The skin is cleansed with alcohol, and is then pinched up ready for the plunge of the needle, which is inserted with the beveled opening pointing outward towards the skin surface. In order to give the tuberculin subcutaneously, the needle is entered through the skin at a very acute angle, and it is advisable to insert it up to the hilt, so that when it is withdrawn no tuberculin will exude through the opening. The reason for keeping the beveled edge of the needle outward is that the tuberculin when leaving the needle may enter the cutaneous tissue, and not the deeper tissues; for, if the tuberculin be injected deeply into the tissues, the resulting local reaction may be much less than when the tuberculin is given just under the skin, and to a certain extent one judges the dosage of the tuberculin by the amount of local reaction. After using the arms for a few injections, one may give the tuberculin in the thighs, back, chest or abdominal wall.

It may now be asked what advantage there is in determining a dose of tuberculin on the basis of a minimal cutaneous reaction, if one does not desire to obtain the reaction produced by tuberculin of the degree indicated in this paper. The method suggested here is not directly applicable save by those who believe in local reaction. At the same time it will allow the determination of a perfectly safe dose, varying at least 100 per cent. in quantity. According to our studies we have determined that in tuberculin dosage there is in individuals a variation of the primary dose from at least 0.000005 to 0.0005 mg. of tuberculin, to produce the same amount of reaction, that is, this method is capable of giving at once an initial dose of tuberculin varying from 0.000005 to 0.0005 mg. of O. T.—a dose varying one hundred times in amount from the smallest to the largest. This forms then a basis for dosage vastly in advance of the former method, when all patients were given doses of tuberculin of

minimal amount in gradually increasing quantities until the point of reaction was reached. In this way it is possible to determine a dose for each case which will produce exactly the same degree of local reaction in all individuals.

TABLE 5.—SHOWING RELATION BETWEEN MINIMAL CUTANEOUS REACTION AND THERAPEUTIC DOSE OF TUBERCULIN

Minimal Cutaneous- Reaction % O. T.	Therapeutic Dose mg. O. T.
0.05	.000005
0.1	.00001
0.25	.000025
0.5	.00005
0.75	.000075
1.	.0001
2.	.0002
3.	.0003
4.	.0004
5.	.0005
6.	.0006
7.	.0007
8.	.0008
9.	.0009
10.	.001

Instead of taking, as in former instances, three, four or five months to reach a dose such as is indicated here, it is possible to reach it within three weeks' time, so that, if there were no gain in the reaction, at least there is a great gain in arriving quickly at the individual dose which the patient can tolerate. We feel that the greatest gain, however, comes in determining the quantity of tuberculin which will give a mild reaction in every individual, and it is only when we get a dose of tuberculin which will produce these mild reactions that we can hope for beneficial results of a curative nature.

We feel that we have offered for the first time in therapy a specific, individual, biological test for therapeutic doses which is, of course, the goal to be aimed at in all therapeutic measures. In other words, instead of giving a dose of a drug which is known to produce a certain physiological effect, in a small number of individuals, it is possible in this way to give exactly the dose of the drug which is best suited to each individual, and this must, in future, be the basis of rational therapeutics.

We are unfamiliar at this time with the causative factors which vary the sensitiveness of the body cells to tuberculin, but we would here add a closing caution that, if sometimes during tuberculin therapy the sensitiveness of the body to the tuberculin changes, it is best to determine the minimal cutaneous reaction before giving another therapeutic dose. In

this way it will be possible to keep the body at about the same reaction to therapeutic doses of tuberculin.

We have found that, as a routine practice, it is well to repeat the skin test for minimal cutaneous reaction every three months; but in pursuing this course, we have come to the conclusion that it is not the tuberculin administered which changes the susceptibility to this poison, but some deeper and more subtle influence.

#### CONCLUSIONS

1. It is just as possible to obtain a constitutional reaction from tuberculin placed on the skin as from tuberculin introduced beneath the skin. Tuberculin reactions, whether local, focal or constitutional, must be looked on as varying grades of the same response of the body to a varying quantity of tuberculin used.

2. In the body in which tuberculosis has developed, the degree of reaction of the surface cells to the poison contained in the different tuberculins depends on (a) depth of scarification; (b) point of application; (c) distribution of lymphatics; (d) readiness of absorption; (e) exact amount of tuberculin used.

3. At times the serum of individual cases contains a substance which is capable of producing a cutaneous tuberculin reaction in individuals who are very susceptible to tuberculin.

4. The interval of dosage varies for the result desired, less than seven days for tolerance, and fourteen or more for retention of the reaction power of the cells.

5. In the majority of patients, if the interval of doses be two weeks or more, the amount of local reaction from the same dose of tuberculin does not change in a period of many months.

6. It is possible by determining the minimal cutaneous reaction to 0.01 c.c. of varying solutions of tuberculin, to state the exact amount of tuberculin which will produce a certain grade of reaction when introduced beneath the skin.

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# THE USE OF PURE LIPOIDS AND ALCOHOLIC EXTRACTS WITH ACTIVE AND INACTIVE SERUM IN THE COMPLEMENT-FIXATION TESTS FOR SYPHILIS\*

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In a comparative study of the Wassermann and Noguchi reactions reported by one of us<sup>1</sup> last year, it was stated that by the Noguchi method many positive reactions were obtained with non-specific serums. The same serums, when they were not inactivated, also gave positive reactions by the Wassermann method. When, however, inactivated serum was used in both methods, these non-specific positive reactions disappeared. As a result of this work, in which an alcoholic extract of syphilitic liver was used as antigen in the same proportion in both methods, it was recommended that inactive rather than active serum be used in the Noguchi method.

Noguchi<sup>2</sup> has since shown that a non-specific fixation of complement occurs with unheated serum, when protein bodies are present in the antigen extract, and that this non-specific fixation does not occur with inactivated serum. He attributes the non-specific positive reactions, reported by Swift, to the fact that, in the alcoholic extracts used as antigen, protein bodies are present in varying proportions. To eliminate such non-specific reactions, he advises the use as antigen of an ether-soluble, acetone-insoluble organ extract which is free of protein.

It is the object of this communication to present the results of a comparative study of the use of the two forms of extract in both the Wassermann and Noguchi methods, the latter being performed with both active and inactive serum.

## DESCRIPTION OF METHODS

*Preparation of Antigens.*—The Ether Extract: The pure lipoid solution was prepared, after the method recommended by Noguchi, from

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\* From the Department of Pathology, the University and Bellevue Hospital Medical College, New York.

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1. Swift, H. F.: The Use of Active and Inactive Serum in Complement Deviation Test for Syphilis, *THE ARCHIVES INT. MED.*, iv, 494.

2. Noguchi, H.: *Proc. Soc. Exper. Med. and Biol.*, 1909, vii, 55.

the liver of a patient who presented evidence of visceral syphilis. The lipid was twice fractionated with acetone. After the first fractionation the solution was found to be hemolytic, but after the second fractionation this hemolytic property disappeared. A saturated solution in ethyl alcohol of this pure lipid was then made; the saturation was carried on for two days at 37° C., after which the preparation was filtered and kept as a stock solution.

**The Alcoholic Extract:** The liver from a case of congenital syphilis was extracted in absolute alcohol at 37° C. for one week. The filtrate of this extract was kept as a stock solution. At the end of six weeks it was noted that this alcoholic extract was becoming weaker in its power of fixation, so another, similarly prepared, was substituted. This retained its strength, and was used throughout the latter part of the series of tests here reported. From these alcoholic stock solutions fresh emulsions in normal saline solution were made each day.

**Standard of Fixation Power:** In preparing and comparing different extracts, used as antigen, it is obviously desirable to have their power of complement-fixation as nearly equal as possible. This is necessary not only for purposes of comparison in any given set of tests, but also, when the effect of treatment is studied over a period of years, in order that new antigens of similar power may be prepared from time to time. The following method has, therefore, been devised for the preservation of a standard of fixation power:

With an efficient antigen of known standard the smallest amount of syphilitic serum that will completely fix the unit of complement is determined. This is called the syphilitic unit. The quantity of syphilitic serum constituting this unit and the unit of the same complement are mixed with decreasing amounts of the new antigen, and thus the minimum amount of the antigen that will completely fix one unit of complement in the presence of one unit of syphilitic antibody is determined. Such determinations are made with a number of syphilitic serums before the final standard is fixed, and this is further controlled by using several negatively reacting serums. In this way the emulsions of the antigens used in the reactions may be brought to equal fixation power.

**Wassermann's Method.**—Quantities one-half of those usually described were used: inactivated human serum, 0.1 c.c.; guinea-pig serum, 0.05 c.c., made up to 0.5 c.c. with normal saline solution; antigen, standard amount made up to 0.5 c.c.; total volume, 1.5 c.c. After incubation for one hour, 0.5 c.c. of a 5 per cent. suspension of sheep cells and two units of antisheep hemolysin made up to 0.5 c.c. are added, and incubation



continued for one hour. The reactions are controlled by the use of a known positive and a known negative serum. The reagents are controlled by combining them in the usual proportions, omitting human serum in one tube and antigen in another. In addition it was determined whether 0.05 c.c. of each suspected serum would hemolyze 0.5 c.c. of the sheep cell suspension in the presence of 0.05 c.c. guinea-pig serum: if, in this control, hemolysis is complete at the end of one hour, it is evident that 0.1 c.c. of the serum contains at least two units of antisheep hemolysin. When this amount of native hemolysin was present, no rabbit's hemolytic serum was added, and it was possible to avoid an excess of hemolysin with a consequent masking of a partial fixation. In all reactions the hemolytic unit was determined each day for both the antisheep and anti-human hemolysins.

#### PROTOCOL

##### PART I. DETERMINATION OF SYPHILITIC UNIT \*

Amount Known Positive Serum, c.c.	Complement, 10 Per Cent., c.c.	Standard Anti-gen Emulsion, c.c.	Procedure.	Result.
0.1	0.5	0.5	Total volume of all made 1.5 c.c.; incubate 1 hour;	--
0.05	0.5	0.5	add 0.5 c.c. 5% sheep cells	++
0.025	0.5	0.5	and 2 units antisheep hemolysin; incubate 1 hour.	++
0.012	0.5	0.5		+
0.006	0.5	0.5		+-

##### PART II. DETERMINATION OF NEW ANTIGEN UNIT †

Amount Known Positive Serum, c.c.	Complement, 10 Per Cent., c.c.	New Anti-gen Emulsion, c.c.	Procedure.	Result.
0.025	0.5	0.6	Total volume of all 1.5 c.c.; incubate 1 hour; add	++
0.025	0.5	0.5	0.5 c.c. 5% sheep cells and	++
0.025	0.5	0.4	2 units antisheep hemolysin; incubate 1 hour.	+
0.025	0.5	0.3		+-
0.025	0.5	0.2		--

\* Usual controls of all reagents in each part of experiment.

† 0.5 c.c. of the new antigen equals 0.5 c.c. of the old antigen.

*Noguchi Method, with Active Serum.*—One capillary drop of suspected serum and 0.04 c.c. guinea-pig serum made up with normal saline solution to 0.4 c.c. were mixed with antigen in the same proportion as in the Wassermann reaction (0.4 c.c. of the freshly prepared emulsion). The total volume was made up to 1.2 c.c. and incubated at 37° C. for one hour, and then two units of anti-human hemolysin made up to 0.1 c.c., and 0.1 c.c. of a 10 per cent. suspension of human cells were added. Incubation was continued for another hour.

*Noguchi Method with Inactive Serum.*—After heating to 56° C. for thirty minutes the serum was used in amounts of 0.08 c.c. The other

reagents were used as in the test with active serum. In the control tube without antigen 0.1 c.c. of the serum was used. The reagents were controlled as described in the Wassermann reaction. The various reactions were all performed with the same complement, so that the results of each set of reactions are comparable.

The antigens were at first used in the same proportion in the Noguchi "active" as in the Wassermann and Noguchi "inactive" reactions. It was found, however, that for the Noguchi "active" reaction it was, as a rule, too strong. Although it was tried out against the serum of several normal persons and gave no reaction, it was found advisable to reduce the amount to three-fourths of that used in the "inactive" method. This gave sensitive reactions with syphilitic serums and did not give so many reactions in non-specific cases.

#### DISCUSSION OF METHODS

In the preparation of antigens the following points are important:

It is desirable: (1) that the extract react with the highest percentage of syphilitic serums and not react with non-syphilitic serums; (2) that it retain its properties unimpaired; and (3) that, with a constant method of preparation, an extract having the same properties be always obtained.

Alcoholic extracts of organs have been used most extensively thus far, and it is the general opinion that an antigen in this form retains a practically uniform strength for many months. Many who have tried the antigen-impregnated papers have noted that the character of their reaction changes after a time. Often the fixing power is much decreased and occasionally anticomplementary action is noted. In studies which are to extend over several months, and in clinics and practice where the effect of treatment on the reaction is to be noted, a single preparation of uniform strength is very desirable. Alcoholic extracts of organs vary in character in the widest degree. From some livers, extracts are obtained that are so hemolytic that they cannot be used. Other extracts may be very anticomplementary in proportion to their fixing power. The ether-soluble, acetone-insoluble solution offers the most efficient antigen. The ether extraction appears to eliminate the anticomplementary properties, and the acetone fractionation surely removes the hemolytic substances of the original alcoholic extract, leaving the lipoids, which are the efficient bodies in the complement-fixation test. It is probable, also, that by this method similar bodies are obtained from different livers, so that the variations noted in the solutions obtained by simple alcoholic extraction are avoided. For these reasons the Noguchi method of antigen preparation appears to be the most desirable one. Only an actual trial of the

two forms of antigen, such as is here presented, can give an idea as to their relative value.

#### DISCUSSION OF RESULTS

Tables 1, 2 and 3 represent the results of the comparative study of the Wassermann and the Noguchi reactions, the latter performed with both active and inactive serum, using both the alcoholic extract and an ether-soluble, acetone-insoluble extract as antigen in 300 consecutive specimens of blood obtained from hospitals, dispensaries, and private practice. The cases are classified according to the stages of syphilis indicated by the diagnoses accompanying the specimens. Cases of leprosy and of doubtful lesions, possibly syphilitic, but giving a positive reaction, are also shown in Table 2. In order that possible sources of error may be indicated, non-specific cases, in which there is little probability of syphilis, but in which weak positive reactions were obtained, are also given individually in Table 3.

TABLE 1.—SYPHILIS, ALL STAGES, TREATED AND UNTREATED; 212 CASES

Stages.	Cases	Antigen.	Wassermann			Noguchi Active			Noguchi Inactive		
			++	+	-	++	+	-	++	+	-
Primary.....	12	I	5	1	4	2	8	3	1	0	5
		II	7	0	4	1	10	1	1	0	6
Secondary.....	44	I	29	5	6	4	38	4	0	2	27
		II	31	8	2	3	37	3	1	3	30
Tertiary.....	56	I	34	4	9	9	40	11	3	2	36
		II	37	4	8	7	41	9	4	2	31
Early Latent.....	31	I	8	2	9	12	12	9	6	4	3
		II	10	1	12	8	14	10	4	3	6
Late Latent.....	61	I	10	3	16	30	21	11	12	17	9
		II	12	5	15	29	22	8	11	20	10
Tabs.....	6	I	..	1	..	5	1	1	2	2	..
		II	..	1	..	5	1	1	2	2	..
Congenital.....	2	I	1	..	..	1	1	..	1	1	..
		II	1	..	..	1	1	..	1	1	..
Total cases.....	212										

In this study no attempt has been made to classify the cases according to the amount of antisyphilitic treatment received, and consequently numerous negative or weakly positive reactions are recorded among the cases classified as frankly syphilitic.

The superiority of the pure lipid over the alcoholic extract is noted in all the methods and in all the stages of syphilis. The Noguchi method with active serum gives the largest number of positive reactions. It appears earlier in the primary stage, and persists longer in the cases under treatment. The Wassermann method gave the highest number of positive reactions, and the Noguchi method with inactive serum the fewest. The difference in the two latter methods is largely one of degree;

TABLE 2.—SUSPECTED SYPHILIS AND LEPROSY; 21 CASES \*

Diagnosis.	Wasser- mann.		Noguchi Active		Noguchi Inactive.		Remarks.
	I A.E.	II P.L.	I A.E.	II P.L.	I A.E.	II P.L.	
Leprosy.....	—	—	+	+	—	—	Anesthetic type. Nastin B injections.
Leprosy.....	—	—	+	+	—	—	Mixed type. Nastin B injections.
Leprosy.....	—	++	++	++	++	++	Nodular type.
Ulcerations at angle of mouth.....	—	—	—	++	—	—	Has had gonorrhea several times. Had 2 months' mixed treatment 4 years ago.
Cystitis, chronic.....	—	—	+	+	—	—	Had gonorrhea 3 times in 2 years. No mercury.
Chancroid.....	—	+-	++	++	+-	+-	No symptoms except local. No treatment except local.
Intractable nose-bleed	—	—	+	+-	—	—	Following incision of membrane. Syphilis in family.
Paralysis of leg.....	—	—	+	+	—	—	.....
Stricture of rectum...	—	—	+	++	—	—	New growth or specific stricture.
Epididymitis, chronic.	—	—	+	++	+	+	Chancroid persisted 40 days after exposure. No secondaries.
Rash.....	—	—	+-	+-	—	—	Herpetic eruption on penis 3 months ago.
Arteriosclerosis.....	—	—	+	+	—	—	Aortic insufficiency. Nephritis.
Psoriasis.....	—	—	+-	+-	—	—	Chancroid 5 years ago. No secondaries. Took pills 2 months.
Headache.....	—	—	+	—	—	—	Worse at night.
Pellagra?; adenopathy	—	—	+-	—	—	—	Chancere? 4 years ago. Had 15 days' mixed treatment recently.
Epididymo-orchitis....	—	—	+	+-	—	—	Two weeks.
Sore on mammary gland.....	+-	+-	+	+-	—	—	Ten days. Very suspicious of chancre. No mercury.
Headaches and dizzi- ness.....	—	—	+-	—	—	—	No mercury.
Cirrhosis of liver. ascites.....	—	—	++	++	—	—	Had gonorrhea.
Asthma and paralysis agitans.....	—	—	+	+	+-	—	Had gonorrhea twice.
Aortic regurgitation..	++	++	++	++	++	++	Had gonorrhea.

\* No definite syphilitic history obtainable.

TABLE 3.—NON-SYPHILITIC, BUT GIVING SLIGHT REACTION; 17 CASES \*

Diagnosis.	Wasser- mann.		Noguchi Active.		Noguchi Inactive.		Remarks.
	I A.E.	II P.L.	I A.E.	II P.L.	I A.E.	II P.L.	
Enlarged cervical glands.....	—	—	+	—	—	—	One month.
Psoriasis.....	—	—	—	+-	—	—	Yearly exacerbations 10 years.
Chancroid, gonorrhea.....	—	—	+	—	—	—	Has had no mercury.
Scabies.....	—	—	—	—	—	—	.....
General furunculosis.....	—	—	—	+-	—	—	.....
Chronic abscess, abdomen.....	—	—	—	+-	—	—	Brother has syphilis.
Rheumatism-endocarditis.....	—	—	—	—	—	—	.....
Varicocele.....	—	—	+	—	—	—	No mercury.
Acute bronchitis.....	—	—	+	+-	—	—	No mercury.
Actinomyces.....	—	—	+-	+-	—	—	No mercury.
Adenopathy.....	—	—	+-	+-	—	—	General enlargement.
Neuritis.....	—	—	+	+-	—	—	Lead? 1 month. No. Hg.
Tumor of pelvis.....	—	—	+	—	—	—	Probably malignant.
Sclerodactylitis.....	—	—	+-	—	—	—	Fingers frozen 20 years ago.
Edema and congestion, left leg	—	—	—	+-	—	—	No mercury.
Condyloma acuminata.....	—	—	—	—	—	—	Of anus, 1 year.
Hodgkin's disease.....	—	—	+	—	—	—	Enlarged cervical glands 7 years.

\* Fifty non-specific cases taken in hospital wards and dispensaries gave uniformly negative results.

TABLE 4.—ANALYSIS OF 300 CASES\*

Character of Cases.	Number of Cases.	Antigen.	Wassermann.						Noguchi Active.						Noguchi Inactive.					
			++		+		+-		--		++		+		+-		--			
			No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Syphilis, all stages, treated and untreated	212	Ale. ext.....	87	41	18	8	44	21	63	30	121	57	39	18	24	12	28	13	71	33
		Pure lipoid.	98	46	19	9	41	11	51	26	126	59	32	15	23	11	31	15	84	39
Suspected syphilis with no syphilitic history. Leprosy, 3 cases.	24	Ale. ext.....	1	3	0	0	1	3	19	94	6	24	9	43	6	28	1	5	2	9
		Pure lipoid.	2	9	0	0	2	9	17	82	7	35	5	24	6	29	3	13	2	10
Non-specific; 50 cases gave negative reactions throughout.	67	Ale. ext.....	..	..	..	..	..	..	67	100	1	1	8	12	8	12	50	75	..	..
		Pure lipoid.	..	..	..	..	..	..	67	100	..	..	..	..	..	..	..	..	..	..

\* Percentages are computed on the number of cases in each group. The three types of reaction using two antigens were done on each case.

when weak reactions are present, the Wassermann method is easier to read, because there are more cells to indicate the amount of hemolysis. Attention has been called by one of us<sup>3</sup> to the relative sensitiveness of the Wassermann and Noguchi methods in repeated examinations for determining the effect of treatment. This point is well illustrated in the table under latent syphilis. As a rule, the cases of latent syphilis have received more treatment than the cases of active syphilis. The sensitiveness of the active serum method is more marked in this stage than any other.

In the table of suspected cases (Table 2) it will be noted that, with the exception of leprosy, those individuals who were the most strongly suspected of syphilis gave the most marked reaction. In either method in which inactive serum was used, a positive reaction practically always was an indication of the presence of syphilis. With the active serum the cases in which there was the least ground for a suspicion of syphilis, the strongest reaction was obtained with the alcoholic extract. The oversensitiveness of the alcoholic extract is also well marked in the cases in which there was little evidence of the presence of syphilis. Weakly positive reactions in such cases, however, are often found with the pure lipid, so that weakly positive reactions have practically no diagnostic or prognostic value. The importance of the use of absolutely fresh serum must be emphasized, for positive reactions obtained with unheated serum three days old have practically no value. We have found it extremely important, as pointed out by Noguchi, to examine the specimens of suspected serum within twenty-four hours, as it has been found that specimens examined one day with negative results give a partial fixation on the following day. This fact, no doubt, explains the reason for a certain number of so-called non-specific reactions with the active serum. With the elimination of these apparent non-specific reactions by inactivating the serum, we feel that more reliable results will be obtained by the use of both active and inactive serum. A negative reaction with active serum gives strong evidence against active syphilis; while a positive reaction with inactive serum speaks more strongly for syphilis than one with active serum. It is, however, only fair to say that, with the pure lipid as an antigen, we have not seen a strongly positive reaction in any case, except leprosy, in which syphilis could be absolutely excluded. Reactions of less degree than "absolutely positive" always are to be regarded with some doubt, unless other symptoms of syphilis or history of the disease can be obtained.

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3. Swift, H. F.: The Effect of Treatment on the Wassermann Reaction. *THE ARCHIVES INT. MED.* (to be published).

## CONCLUSIONS

1. The "pure lipoid" antigen (ether extract) has proved the more satisfactory. It has given, with syphilis, the largest percentage of strongly positive reactions by all three methods.

2. The alcoholic extract antigen, when used with active serum, has given the largest percentage of non-specific reactions.

3. Inactivation apparently destroys the power of a non-specific serum to cause a positive reaction.

4. The Noguchi method, using active serum, gives the most sensitive reaction in syphilis; the Wassermann and the Noguchi "inactive" methods stand in the order named.

5. One of the most important factors in securing reliable results, when active serum is employed, is the performance of the reaction within twenty-four hours after the serum is obtained.

For the use of the clinical material upon which this report is based, we wish to thank Drs. Fordyce, Brooks, Van der Poel, Stevens, Nordemann and Keane of the University clinic.

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# THE WASSERMANN REACTION IN THE PATHOLOGY, DIAGNOSIS AND TREATMENT OF SYPHILIS \*

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## INTRODUCTION

Metchnikoff, in his preface to the recent treatise of Levaditi and Roché on experimental syphilis, compares the evolution of our knowledge of syphilis to the three phases of the development of human thought as established by Comte: the theological, the metaphysical, and the scientific. He sketches briefly the history of syphilis through its first period, that of superstition, in which the only advance was the discovery of the specific remedy, mercury; through the second period of empirical medicine with its thorough clinical studies of the varied manifestations of syphilis and the recognition of gonorrhea and chancroid as disease entities; and through the period represented by the past half-decade of scientific investigation, during which the experimental transmission of the disease has been demonstrated, the etiology determined and a method of serum diagnosis established.

He makes the statement, somewhat pardonable in one so largely responsible for our new knowledge of the disease, that the study of syphilis, until now purely clinical, has become so much a matter of laboratory method that the diagnosis can be made without seeing the patient by the simple examination of his blood or of the secretions from his lesions. Be this as it may, it is not my intention to laud the achievements of the laboratory or to go into detail concerning its methods as applied to syphilis. I do wish, however, to demonstrate that these methods are destined ultimately to establish the pathology of syphilis on a sound basis, to afford thereby a clear insight into many obscure conditions heretofore but imperfectly understood clinically and to result eventually in a rational therapy.

The methods at hand are (1) the recognition of the *Spirochæta pallida*, which we owe to Schaudinn and Hoffman (1905); (2) the experimental production of the disease by inoculation, as first clearly

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shown by Metchnikoff and Roux (1903); and (3) the method of serum diagnosis with which we associate especially the names of Wassermann, Neisser and Bruck (1906). The first and second of these I shall discuss briefly, as their use is practically limited to the primary and secondary manifestations of the disease. It is of the more obscure manifestations of late syphilis affecting the cardiovascular and nervous systems, the bones and joints and the organs of special sense, to which can be applied only the method of serum diagnosis that I wish especially to speak. It is to this phase of the subject that I shall give most of my time, but, in order to round out my presentation, a few words may be said concerning the results of animal inoculation and the distribution of the *Spirocheta pallida*.

It is a tribute to past generations of syphilographers that the conclusions which they reached concerning many of the problems of infection, extension of the virus, acquired immunity, etc., have been confirmed by our present knowledge of experimental syphilis and of the distribution of the spirochete, as have also, through the use of the Wassermann method, many conclusions of the pathologist concerning the chronic lesions more or less frequently found in individuals with syphilitic history. It is no mean triumph that the views concerning a disease of unknown etiology, based on clinical and pathological observations, should have been thoroughly supported when the causative agent of the disease was discovered and its distribution in the tissues and fluids of the body determined.

In the first place, a word may be said as to the importance of the experimental work in the establishment of syphilis as essentially a disease of man, and incidentally confirming man's blood-relationship to the higher apes. Although it has been asserted that lesions similar to the chancre have been produced in various animals, no disease at all comparable to syphilis was ever produced in animals until the ape was used. In view of our comparatively recent knowledge of the blood-relationship of various animals, as definitely established by the use of the biological blood test (precipitin test), this is not surprising. But even to one familiar with zoological relationships, it is interesting to note the varying susceptibility of various members of the monkey family to syphilis. As Metchnikoff and Roux clearly brought out in their first communication on experimental syphilis, success or failure depends chiefly on the species of monkey used. Neisser has shown that this depends on the position of the species in the zoological series, the higher monkeys (chimpanzee, gorilla, orang-outang), nearest to man in the animal scale, take syphilis typically and present the primary and secondary lesions as they occur in man, that

is, chancre, enlarged glands, secondary eruption and mucous patches. The lower monkeys react locally only, while the gibbon, which is intermediate in the scale, gives atypical primary and secondary lesions. It is evident, therefore, that the production of syphilis in the anthropoid apes was not merely a matter of demonstrating that an animal susceptible to the virus of syphilis had been found. Such information would have been of no more aid to us than our present knowledge that the rabbit is susceptible to infection with the pneumococcus, which organism does not produce a typical pneumonia in this animal. The experiments on apes showed not only the possibility of reproducing syphilis with its primary lesions and many of its secondary manifestations in typical form, but—and this is of greatest importance—of reproducing these lesions in an animal so closely related to the human species that conclusions reached for simian syphilis could be applied immediately to the disease in man. Man was no longer the only animal available for observations on the nature of syphilis and experiments in therapy. The anthropoids, on account of their close blood-relationship, became available for experiment, and many investigations impossible on man could be undertaken. Much has been accomplished. Among other things it has been found that only when the virus is inoculated into the skin proper, either by deep scarification or into actual pockets in the skin, could the disease be produced. Inoculation into the subcutaneous tissues, into the blood-vessels or into the peritoneal cavity all fail. It is evident that the spirochete finds conditions for initial propagation only in the skin, and that there it must undergo a certain degree of development before the general invasion of the blood occurs or the local lesion appears. On the other hand, the invasion of the blood may occur before the appearance of the initial lesion, which is in accord with our clinical experience concerning the futility of early excision of a chancre. This is demonstrated in experiments on monkeys, in which it was found that as early as the fifth and eighth days after inoculation the virus is present in the blood and can produce local lesions in other monkeys. Thus, the blood of an animal in which chancre was not evident until the twenty-second day was found to be virulent on the fifth day; in another, in which chancre developed on the twenty-eighth day, the blood was virulent on the eighth day.

Experimental syphilis also throws light on the question of the localization of the virus during the florid period of syphilis, and especially during the quiescent periods which separate the active stages. Of all organs in the infected animal capable of transmitting the disease, infection follows most frequently after inoculation with the bone-marrow, the spleen, the

lymph-nodes and the testicle, in the order named. The localization in the first three of these, all hematopoietic organs, reminds one of the localization of the malarial parasite during certain stages of its development. As Neisser has found these tissues to be capable of transmitting the disease after nearly 300 days, there can be little doubt of their importance in the preservation of the spirochete. As to the predilection of the spirochete for the testicle it is not surprising to find that this localization has been invoked as an explanation of the transmission of hereditary syphilis, it being assumed that the transmission occurs in the semen, with infection of the ovum, but no infection of the mother. In this connection it is noteworthy that Finger and Landsteiner have produced syphilis in the monkey with the sperm of a syphilitic.

As to the presence of the virus in the circulating blood of man, there is little evidence. Experimental inoculations of the monkey have given positive results in a few instances in which the blood has been taken from individuals in the first two months of the disease, but they have usually been unsuccessful. Likewise, it has been found extremely difficult to demonstrate the spirochete by direct examination of the blood. It is necessary to conclude, therefore, that although it may occasionally occur in the peripheral circulation, it is localized for the most part in the bone marrow and spleen.

Experimental syphilis also explains the relative infrequency of infection from contact with tertiary lesions. While monkeys may readily be infected with material from chancre and mucous patches, inoculation with material from tertiary lesions has seldom been successful. There is, however, some evidence at hand that the spirochete may exist in some tertiary lesions in very small numbers. This conclusion is supported by the experience of those who have made a search for the spirochete in such lesions by direct examination.

Of extreme importance, in view of the well-known involvement of the vascular structures in syphilis, is the histological observation that in all early lesions of syphilis the spirochete is found most abundantly in the cell accumulations in and about the blood-vessels and lymphatics, and is presumably directly responsible for the endothelial and perivascular changes so characteristic of the disease and which explain so much of its pathology.

#### THE WASSERMANN REACTION

As the diagnosis of syphilis by the recognition of the spirochete is limited to the primary and secondary lesions, the internist and the specialist interested in the late lesions of syphilis must have recourse to the

method of serum diagnosis as described by Wassermann, Neisser and Bruck. Although the literature of this diagnostic method is now enormous, its use in this country has been limited to a few medical centers and its general importance has not, I am sure, been thoroughly appreciated by the profession at large; nor have the results of its use been presented, from the clinical point of view, in comprehensive form. My interest was first stimulated by the work on this subject carried out in my laboratory at New York University during the past two years by one of my assistants, Dr. Homer F. Swift. Day by day I have followed his results, impressed by the constancy with which a positive reaction supplemented definite clinical diagnosis, now and then amazed by the marvelous success of the reaction in clearing up the diagnosis of obscure or doubtful syphilitic conditions, and finally I have been forced to the conclusion that in this method we have, at last, the means not only of clearing up the pathology of many phases of syphilis, but of establishing definite rules for treatment, and, apparently, as recent work indicates, of recognizing complete cure. I shall therefore outline the work which has been accomplished, emphasizing the importance of this method in medicine, in surgery, and in the various specialties; its relation to certain conceptions of syphilis hitherto considered fundamental, as those embraced in Colles' law, and shall conclude with a discussion of the importance of the reaction in controlling treatment.

TABLE 1.—OBSERVATIONS ON SYPHILIS IN VARIOUS STAGES

Observer.	Primary —Syphilis—		Secondary —Syphilis—		Tertiary —Syphilis—		Early Latent —Syphilis—		Late Latent —Syphilis—		Hereditary —Syphilis—	
	No. of Cases.	Per Cent. +	No. of Cases.	Per Cent. +	No. of Cases.	Per Cent. +	No. of Cases.	Per Cent. +	No. of Cases.	Per Cent. +	No. of Cases.	Per Cent. +
Collected by Noguchi *	416	69.8	1605	89.1	581	78.1	1233	51	861	47	125	94.5
Noguchi †	70	92.8	197	96	177	89.9	115	75.6	150	79.3	17	100
Swift	21	81	137	97	83‡	89	79	76	94	46	14	86
Kaplan	138	90	281	86	191	73	Latent				20	90
Collected by Bruck §	520	64.4	1301	71-100	512	63-100	1549		47.5		..	....
Bruck, Stern, Merz and Grosser	111	72.1	528	94	224	73.6	867		30.5		..	....

\* Ten observers.

† By Noguchi modification.

‡ Cutaneous lesions of tertiary syphilis; in a second group of fifty-two cases of visceral syphilis positive results were obtained in 79 per cent.

§ Twenty-one observers.

The time at my disposal will not allow of a discussion of the principles and technic of the Wassermann reaction. For such information I refer you to the numerous communications on this subject, and more especially

to those of our own workers, Noguchi, Swift, Kaplan, Fox and Gay and Fitzgerald. I shall, however, in order to demonstrate the efficiency of the test, present a tabulation of extensive observations in primary, secondary, tertiary, latent and hereditary syphilis (Table 1):

With Table 1 may be compared Table 2, which includes the reaction in individuals in whom syphilis could be excluded by history or clinical symptoms with a fair degree of certainty.

TABLE 2.—REACTION IN NON-SYPHILITIC CASES

Observer	No. of Cases	No. +	Per Cent. +
Swift .....	272	3	1.1
Noguchi .....	333	12	3.6
Bruck's collected cases .....	4,432	57	1.2
Bruck, Stern and Merz .....	596	2	0.3
Matson .....	313	1	0.3

\* 33 observers.

These figures give some idea of the results in large series. Many of the individual series are, however, more striking. Thus, in primary syphilis we frequently find reports of 90 to 98 per cent. positive results; in secondary lesions, 100 per cent. (Boas in 393 cases), with never less than 80 per cent.; in tertiary syphilis the figures vary from 60 to 100 per cent., and in hereditary syphilis, they are uniformly high, 70 to 100 per cent. The highest and most constant results are obtained in secondary and hereditary syphilis; the most irregular in primary and latent. It is evident that these variations depend on many factors, as technic, the influence of treatment and, especially in primary syphilis, on the length of time which has elapsed since infection; it is noteworthy that early cases are frequently negative. Also the view is now definitely established that in late syphilis treatment causes the reaction to disappear.

In Swift's experience all cases of syphilis react by the end of the fourth week after the appearance of the chancre, so that in doubtful cases a diagnosis is possible two weeks before the appearance of the roseola. The earliest reaction is reported by Lesser, who found the blood positive eight days after exposure; fourteen days later an initial lesion appeared, and six weeks afterward a typical roseola. Experiments on apes (Bruck) indicate that a positive reaction is evidence of general invasion of the body, and with this is correlated the observation that the ape resists reinfection after a positive reaction.

If this interpretation is correct, one might assume that with the demonstration of the spirochete in the primary lesion and a negative Wassermann reaction, excision of the initial lesion might prevent or

modify the subsequent course of the disease. Theoretically, this would appear possible, but experience indicates that this result is rare.

In other diseases than syphilis, the reaction occurs in leprosy, scarlet fever, yaws (frambesia), and trypanosomiasis frequently, and, to a slighter extent, with tuberculosis, carcinoma and certain diseases of the blood, conditions which, with the exception of yaws, however, are not usually confounded with syphilis and for which we have definite diagnostic methods.<sup>1</sup>

That the Wassermann reaction should be positive in yaws, a disease due to a spirochete and frequently confounded with syphilis, is a matter of biological interest, but not of diagnostic importance in northern countries, in that yaws is essentially a disease of the tropics. As to scarlet fever, it may be pointed out that with convalescence from scarlet fever the positive reaction disappears, whereas in syphilis it persists. The occasional positive reaction in tuberculosis, cancer and diseases of the blood appears to be dependent in some instances on a condition of profound cachexia, in others the condition may be syphilis ignorata.

With this demonstration of the diagnostic value of the Wassermann reaction, a method which should be in use in every modern clinic and in every state and municipal laboratory, we may turn to a consideration of those lesions of general interest to the internist.

#### THE NERVOUS SYSTEM

An early application of the Wassermann reaction was naturally made to the well-known metasymphilitic affections, tabes and general paralysis. As a result, not only has the general opinion concerning the syphilitic nature of these affections been confirmed, but many suggestive observations concerning the possible relation of syphilis to other diseases of the nervous system have been made.

The results of the more important investigations of tabes and general paralysis, covering large series of cases, are shown in Table 3.

It will be seen that in general paralysis the average of positive results obtained by the various observers is about 80 per cent., with extremes

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1. Positive results in leprosy vary from 10 to 70 per cent. Noguchi has collected from the reported results eighty-six cases of leprosy, of which 72.4 per cent. gave positive results. The results for scarlet fever vary from 1 to 50 per cent. of positive or doubtful results according to various observers. The cases collected by Fuá and Koch give 12 per cent. of positive results in 353 cases, though in fifty-nine cases which they examined no positive results were obtained. Swift has analyzed 562 examinations by various observers and finds 5 per cent. of positive results.

of 49 and 100 per cent. The most remarkable results are those of Plaut, Boas and Lesser, each with 100 per cent. of positive reactions in 156, 62 and 42 cases, respectively. In tabes the percentages are lower, with, however, an average for all investigators of 65 per cent., the extremes being 41 and 83.

TABLE 3.—INVESTIGATIONS OF TABES AND GENERAL PARALYSIS

Observer.	General Paralysis				Tabes			
	Blood Serum.	Cerebrosp. Fl.	Blood Serum.	Cerebrosp. Fl.	Blood Serum.	Cerebrosp. Fl.	Blood Serum.	Cerebrosp. Fl.
	No. Cases.	Per Cent. Positive.	No. Cases.	Per Cent. Positive.	No. Cases.	Per Cent. Positive.	No. Cases.	Per Cent. Positive.
Lederman .....	23	87	...	...	68	76	...	...
Hoehe .....	30	80	...	...	45	60	...	...
Schütze .....	...	...	...	...	79	65	29	83
Boas .....	42	100	...	...	20	80	...	...
Lesser .....	62	100	...	...	61	56	...	...
Sachs .....	31	68	...	...	28	64	...	...
Plaut .....	156	100	147	95	14	79	11	64
Stertz .....	45	89	...	...	...	...	...	...
Marie, Levaditi and Yamanouchi .....	27	59	30	93	...	...	...	...
Eichelberg .....	...	...	61	93	...	...	49	56
Raviart, Breton and Petit .....	...	...	72	93	...	...	...	...
Smith and Chandler .....	10	90	64	59	...	...	...	...
McCampbell and Rowland .....	50	96	50	84	...	...	...	...
Noguchi * .....	...	...	...	...	22	41	...	...
Noguchi † .....	15	87	...	...	125	68	...	...
Swift .....	3	66	...	...	54	62	...	...
Kaplan .....	61	65	...	...	205	60	...	...
Rosanoff and Wiseman † .....	75	49	57	76	...	...	...	...
Totals .....	630	81	424	85	721	65	89	68
		(Average)		(Average)		(Average)		(Average)

\* Original Wassermann method used. † Noguchi's modification used.

There has been some discussion about the relative frequency of the reaction in the blood and in the cerebrospinal fluid in cases of tabes and paralysis. Table 4, taken from Noguchi's collected data, shows but slight difference, though individual workers vary somewhat in their results. (Compare Table 3).

TABLE 4.—REACTION IN BLOOD AND CEREbroSPINAL FLUID

	Blood Serum		Cerebrospinal Fluid	
	Cases	Per Cent.	Cases	Per Cent.
General paralysis .....	498	88.1	432	90.
Tabes .....	216	62.66	52	56.2

An important question is that concerning the interpretation of a negative reaction with the cerebrospinal fluid when the blood serum is positive. Some investigators insist that, as any syphilitic affection may give a positive reaction with serum, it is necessary to have the cerebrospinal fluid positive also to be sure of a diagnosis of general paralysis or tabes. This question must be considered for the present as undecided.<sup>2</sup>

The results in cerebrospinal lues vary from 16 to 88 per cent. The figures collected by Noguchi give an average of 47.6 per cent.; Swift obtained 54 per cent. of positive results in eleven cases clinically diagnosed as cerebrospinal syphilis, and in 66 per cent. of nine cases clinically termed syphilitic meningitis. The percentage of positive results obtained by all investigators is as a rule lower than in general paralysis and tabes. If, however, the figures for these three groups are compared with the series in Table 5 representing psychiatric cases in which there was no evidence of syphilis or metasyphilitic disease, the importance of the Wassermann reaction in the study of diseases of the nervous system becomes evident.

TABLE 5.—REACTIONS IN PSYCHIATRIC CASES

Observer	Character of Cases	Number	Positive	Doubtful
Plant .....	Psychiatric	95	4	0
Noguchi .....	Psychiatric	140	20*	12*

\* Twelve of the cases with positive and nine with doubtful reactions were epilepsy.

Some confusion, however, is caused by certain forms of psychiatric disease of non-syphilitic origin, which give a fair proportion of positive reactions. This is seen in Table 6, a summary abstracted from one of Noguchi's tables.

TABLE 6.—MENTAL DISEASE OF NON-SYPHILITIC ORIGIN

Clinical Diagnosis	No. Cases	Syphilis Known	Reaction Positive	Reaction Doubtful	Reaction Negative
Alcoholic psychosis.....	9	4	2	3	4
Dementia præcox.....	131	5	15	17	99
Manic-depressive insanity..	14	1	2	3	9

To what extent these positive reactions are due to unrecognized cerebrospinal or latent syphilis, it is difficult to say. The same is true of suggestive results obtained in the study of idiocy, epilepsy and various

2. For a discussion of the relative importance of the Wassermann reaction, the cytological and globulin methods, see Noguchi, McCampbell and Howland and Rosanoff and Wiseman.



dementias; thus Raviart, Breton and Petit obtained positive reactions in 76 of 246 cases of idiocy or imbecility, with and without epilepsy; in 5 of 31 cases of epilepsy alone; in 3 of 5 cases of senile dementia, and in 5 of 19 cases of dementia præcox. Roubinovitsch and Levaditi in dementia præcox obtained positive reactions in 3 of 15 cases; Noguchi, in the study of 69 cases of epilepsy, had positive results in 12 and doubtful in 9; Rosanoff and Wiseman in epileptic psychoses in 13 of 73 cases; in dementia præcox in 21 of 122 cases, and in manic depressive insanity in 4 of 21 cases. These and other reports of occasional positive results in idiots (Bergmann, Frankel-Heiden, Knoepfelmacher and Leindorf) have led to special investigations of the Wassermann reaction in this group of diseases. The results cannot as yet be definitely stated. One investigation, however, that of Kellner, Clemenz, Brückner and Rautenberg, who have studied 216 idiots of various types, is fairly conclusive. They obtained a positive Wassermann reaction in nine cases, but all except one of these occurred in a group of sixteen cases with definite clinical evidence of hereditary syphilis. It is evident, therefore, that idiocy may be frequently associated with hereditary syphilis, but, on the other hand, syphilis is not so frequent a cause of idiocy as has been heretofore held. The same is true also of epilepsy and the dementias, which give 20 to 40 per cent. of positive results. The percentage is too low to assume that these conditions are usually of syphilitic origin, but it indicates rather that they are associated occasionally with hereditary or acquired syphilis.

Other conditions in the central nervous system giving a positive Wassermann reaction are apoplexy and hemiplegia, as observed by Marie, Levaditi, and Yamanouchi in 3 of 6, by Hoehne in 3 of 7, and Swift in 10 of 12 cases; chronic internal hemorrhagic pachymeningitis (Pick and Proskauer), multiple sclerosis (Nonne, Eichelberg, Swift) and myelitis (Citron, Swift).

It is evident from this summary that the Wassermann reaction has been of value in corroborating opinions concerning the relation of syphilis to tabes and general paralysis and that these diseases may now be regarded as metasymphilitic manifestations. It also promises to be of great value in the diagnosis of other forms of syphilis of the nervous system. As Sachs has pointed out, any method which will differentiate between disseminated sclerosis and multiple cerebrospinal syphilis, or central gliosis and syphilitic central myelitis, or between malignant tumor of the brain and gumma, is most welcome. In this connection, Sachs states that the method should be practiced in every neurological ward as a guide to therapeutics, and adds that no operation should be done in a case of sus-

pected tumor without a Wassermann test. He also speaks of the value of the test in doubtful cases of hemiplegia and in cases of mysterious epilepsy beginning late in life. A negative reaction he regards as of almost as great value as a positive reaction, and is influenced accordingly in his treatment.

#### THE CARDIOVASCULAR SYSTEM

It has long been recognized by the clinician and by the pathologist that certain affections of the vascular system are as constantly associated with syphilis as are the so-called metasyphilitic affections of the nervous system. Aortitis, aneurism and aortic insufficiency represent the group of conditions which clinically have been considered as frequently syphilitic. The relation of aneurism to syphilis we find emphasized in the writings of all able observers. Thus in the sixteenth century Ambroise Paré suggested the relation of syphilis to aneurism, and Osler, in his Schorstein Lecture, refers to Fernelius, a contemporary of Vesalius, who described a venereal form of aneurism; Lancisi in 1728, and Morgagni in 1761, recognized the great influence of syphilis, as did also many Italian physicians of the seventeenth and eighteenth centuries. In recent times the association of aneurism and syphilis was brought out most prominently by F. H. Welch who, in 1875, found that in fifty-six cases of fatal syphilis among English soldiers aortic disease was present in 60.7 per cent. and aneurism of varying grades in 32 per cent. In thirty-four cases of fatal aortic aneurism, there was a syphilitic history in 50 per cent., without other etiologic factors for the causation of aneurism. Welch also recognized the fact that the aortitis of syphilis was different macroscopically from ordinary arteriosclerosis.

The most definite advance, however, in our knowledge of aortic syphilis dates from 1885, and is due to the work of Heller and his associates (Doehle, Backhaus, Phillipe, Moll and Eisenberg) in Kiel. Until this time the lesions of the aorta known under the general head of arteriosclerosis or atheroma had been considered more or less as an entity and due to various causes of which syphilis was only one. It is true that Köster, in 1875, had described a chronic mesarteritis, which he considered the essential factor in aneurism, and that Heiberg, in 1877, had advanced convincing evidence of a lesion occurring in comparatively young individuals, affecting especially the arch of the aorta, limited almost entirely to the media and due to syphilis, but it is from Doehle's first publication from the Kiel laboratory that the detailed study of syphilitic aortitis dates. As described by the Heller school, it is a mesaortitis involving especially the arch of the aorta, characterized by the presence of fleshy

nodules, involving media and adventitia, with cellular infiltration about the vasavascularum and the presence in the media of focal areas of necrosis, by some (Laveran) considered to be gummatous. Later the formation of cicatricial tissue leads to scarring, with either thickening or shrinkage of the vessel wall. The intima is unchanged or involved only secondarily; calcification and atheromatous ulcers are infrequent. It is the injury of the media that predisposes to aneurism, and Heller makes the statement that syphilitic aortitis is the cause of aneurism in 90 per cent. of all cases. Numerous confirmations of these observations appeared, the most important of which are Puppe's study of sixteen aneurisms, three of which he ascribed to ordinary atheroma, one to senile atrophy and the remaining twelve, all in young people, to progressive mesarteritis; and Straub's investigation of aortitis in eighty-four persons dying of progressive paralysis, in sixty-nine of whom he found syphilitic aortitis.

In 1903 the question was thoroughly discussed by the German Pathological Society when Chiari distinguished two types of aortic diseases, one of which he termed "Form A," the usual lesion of arteriosclerosis, an endarteritis with primary changes in the intima, and the other "Form B," corresponding to Heller's "mesaortitis syphilitica," but which he termed "mesaortitis productiva." This latter he found in sixteen of twenty-seven individuals (59 per cent.) in which syphilis was established by clinical or anatomical diagnosis, or by both, and in which arterial disease was present; in the other eleven cases endarteritis ("Form A") was found. Moreover, mesaortitis was found in a further group of twenty cases of probable, but not definitely established syphilis, in fourteen of which, however, progressive paralysis was present. Chiari further states that mesaortitis was found in 47 per cent. of all cases of progressive paralysis which he examined. Aneurism occurred in four of the individuals with the medial disease and in three with the intimal form.

Chiari concludes that mesaortitis frequently accompanies syphilis and may be caused by it; that it is most frequent in younger individuals and is associated with aneurism and with narrowing of the coronary arteries. He implies, however, that syphilis may not be the sole cause of mesaortitis, and apparently for this reason uses the term "mesaortitis productiva" instead of Heller's earlier term "mesaortitis syphilitica." At the same meeting Benda brought forth evidence to indicate the syphilitic nature of the necroses (miliary gummata), in the early vascular lesions, of the transition of such lesions to the late scarring, and of the relation of this sequence of lesions to aneurism.

Since this exposition, mesaortitis has had a very definite standing as a type of aortitis, presumably due to syphilis and distinct from endarteritis deformans. This view is supported by the studies which Weisner, Bruhns and Klotz have made of congenital syphilitic aortitis, which they find is a disease of the outer layers of the media and adventitia, quite analogous to mesaortitis in acquired syphilis. The verdict, however, is not unanimous. Marchand, while admitting that mesaortitis may be associated with syphilis, is not convinced that the lesion is histologically specific and adheres to his earlier opinion that the majority of aortic aneurisms are caused by the ordinary form of arteriosclerosis. In this country also, Ophüls considers arteriosclerosis of the aorta to be a unit; the disease affecting all coats, but involving at times one coat more than the others. He does not deny the importance of syphilis as an etiologic factor, but believes in the unity of the disease, anatomically, "even if in some cases the syphilitic virus should be eventually demonstrated in the lesions."

It is of interest that, at the time of this declaration, the spirochete of syphilis had already been demonstrated in mesaortitis. Ophüls' communication was published in June, 1906; in the preceding April appeared a note by Reuter concerning the finding of the spirochete in a mesaortitis of the Heller type. This was followed by similar communications by Benda, in July of the same year, and by Schmorl in January, 1907. During the past year (1909) Wright and Richardson have found the spirochete in five cases of syphilitic aortitis. Owing to the possible error of confusing degenerated tissue fibrils with the spirochete, and also owing to numerous negative findings, the earlier reports were received with some skepticism, but it is noteworthy in this connection that Schaudinn, to whom Reuter's preparations were shown, confirmed the finding of the spirochete, and Reuter's illustrations in his second communication are very convincing. Benda found the spirochete in a cerebral artery in tertiary syphilis, the vessel lesion being characteristic of fresh arterial syphilis, spirochetes, both typical and granular, being found in a focus in the outer portion of the media. Levaditi and Roché, in their monograph on "Experimental Syphilis," state that one of them had examined Benda's preparations and was convinced of the identity of the organisms with the *Spirochæta pallida*. Schmorl found the organisms in a mesaortitis of tertiary syphilis, as did also Dr. Oscar Klotz.<sup>3</sup>

In the five cases of Wright and Richardson the ages of the individuals varied from 30 to 43. An aortitis limited mainly to the ascending por-

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3. Quoted by Osler; confirmed by personal communication.

tion and arch was common to all, as were also well-marked fibrous changes in the aortic valves, the other valves not being affected. The coronary arteries were not remarkable except in that their orifices were more or less occluded by the fibrosis in the walls of the sinuses of Valsalva. Hypertrophy and dilatation of the heart occurred in three, and aneurism in one. The aortitis was of the type usually described as syphilitic; calcification of the aorta or the aortic valves was found but once. Necrosis of the media was common to all five cases, and it was in this necrotic material that spirochetes were found. In only one instance were spirochetes found in a granulomatous area. The number of the organisms varied greatly in the different aortas and in different places in the lesions. They were not found in all necrotic areas, and when present were usually few in number, though in one case they are described as fairly numerous and in another as present in enormous numbers. In two cases atypical forms predominated, but as similar atypical forms were found not only accompanying typical spirochetes in other cases but also in the livers of congenital syphilis, they conclude that these were degenerated spirochetes. Although these investigators state that they are not thoroughly convinced of the identity of these forms with the *Spirochata pallida*, their control observation, including a careful study of tissue fibrils, leaves no other conclusion. From their description and drawings the organisms appear as typical as any found in congenital syphilis.

Perhaps the most important observation which they make, in that it has a bearing on the etiology of mesaortitis, is that concerning the relation of the spirochetes to the necrotic areas. "The finding of the spirochetes in an area of primary necrosis in the media, as well as in association with the necrosis in the fibrous tissue, seems to justify the belief that the microorganisms are the cause of the necrosis by their local action on the tissue and that they are to be regarded as the cause of the whole process, although the possibility that they may be merely secondary invaders cannot be denied. Their numbers and distribution in the lesions would suggest that they rapidly multiply at a given point, produce necrosis and then degenerate and disappear."

In view of such evidence, it is difficult to deny that the mesaortitis found under such circumstances is a lesion of syphilis due to the local action of the *Spirochata pallida*. We may confidently expect further observations to confirm this view.

#### AORTIC INSUFFICIENCY

Although the spirochete has been demonstrated only in mesaortitis, we have other evidence, that based on the method of serum diagnosis, to indi-

cate that various lesions of the vascular system may be caused by syphilis. Most of the work by this method has had for its object the demonstration of the syphilitic origin of aortic insufficiency. That syphilis is a common cause of aortic insufficiency is a matter of common clinical knowledge, and pathologists have long been aware of its frequent association with the mesaortitis ascribed to syphilis. Indeed, recent investigation seems to show conclusively that the lesion of the valve is an extension of the disease in the aortic wall. Numerous statistics based on clinical and pathological observation are available, and of these a few may be given. Thus, Saathoof has emphasized the close relation of aneurism and aortic insufficiency to syphilis, and describes seven cases of luetic aortitis, in six of which aortic insufficiency was present. Mönckeberg analyzed thirty cases of mesaortitis, in eleven of which there was a definite history of syphilis. Narrowing or occlusion of the coronary arteries occurred in eight, aortic insufficiency in thirteen, and aneurism in ten. He further states that fully 33 per cent. of published cases of mesaortitis offer a history of syphilis, and of the remainder 44 per cent. are associated with metasymphilitic conditions. Citron has shown that in thirty-five cases of pure aortic insufficiency, a definite history of syphilis was present in 14.2 per cent. and a history of probable syphilis in 25.7 per cent. His results with the Wassermann reaction, as will be shown later, give syphilis a most prominent place in the etiology of this lesion.

The subject has recently been investigated clinically and pathologically by Longcope, who has utilized the material of the Pennsylvania Hospital. In a series of 930 autopsies, seventy-six cases of chronic aortic endocarditis were found. Twenty-one of these were unassociated with lesions of any of the other valves and constantly accompanied by mesaortitis, which was always confined to the arch of the aorta, sometimes extending only a few centimeters from the aortic cusps. The gross and histological lesions of the aorta in all cases were those of syphilitic aortitis. Aneurism was present in four; calcification in one case only. Moreover, in those cases in which the valves were studied histologically the process in the aorta could be followed to the attachment of the cusps, and in the cusps certain features of the histological lesions of mesaortitis could be found. In eleven of the individuals, all of whom were young or middle-aged, there was a definite history of syphilis or the diagnosis was established by finding gummata at autopsy. Eighteen of the twenty-one gave clinical evidence of aortic insufficiency.

In a second group of twenty-one cases with clinical evidence of aortic insufficiency but with other valves also affected, lesions of the aorta were

absent. These were, for the most part, in young persons with, as a general rule, a history of rheumatic fever.

In a third group of thirty-four cases, in which the aortic valves alone were affected, no mesaortitis existed. They were for the most part elderly individuals, and in all but nine the intimal type of arteriosclerosis or endarteritis deformans characterized by calcification, was present. In only four were signs of aortic insufficiency present during life.

These results may be expressed in tabular form (Table 7).

TABLE 7.—AORTIC ENDOCARDITIS

	Pure with Me-aortitis	Pure with Endarteritis	Other Valves and Rheumatism
Aortic insufficiency.....	18	4	21
No aortic insufficiency.....	3	30	9

Thus it is seen that a pure aortic endocarditis with insufficiency is in the great majority of cases associated with me-aortitis and is presumably of syphilitic origin.

To this anatomic evidence of the importance of syphilis in vascular disease may be added that obtained by the use of the Wassermann reaction, as presented in Table 8.

TABLE 8.—WASSERMANN REACTION IN CARDIOVASCULAR LESIONS

Observer.	Aneurism.		Aortic In-		Other Valv-		Mesaortitis.		Arteriosclero-	
	No.	Posi- tive.	No.	Posi- tive.	No.	Posi- tive.	No.	Posi- tive.	No.	Posi- tive.
Kroner .....	1	1	1	1	1	1	1	1	1	1
Citron .....	16	10	16	10	3	1	1	1	1	1
Schütze .....	3	3	6	5	1	1	1	1	1	1
Danielopolu .....	2	2	2	2	1	1	1	1	1	1
Laubry and Parvu..	6	4	6	3	14	3	10	5	1	1
Donath .....	3	3	23	19	14	3	9	8	1	3
Collins and Sachs..	5	5	13	10	14	3	1	1	1	1
Swift .....	3	1	12	6	1	1	1	1	1	1
Hoehne .....	3	1	2	1	1	1	1	1	1	1
Noguchi .....	1	1	1	1	1	1	1	1	1	1
Clough* .....	29	10	9	6	1	1	1	1	1	1
Bellner and Mus- catello .....	1	1	1	1	1	1	1	1	1	1
Beckers .....	2	2	2	2	1	1	1	1	1	1
Hasenfeld and Szili	1	1	1	1	1	1	1	1	1	1
Löhlein † .....	1	1	1	1	1	1	1	1	1	1
Fränkel and Much†	4	2	1	1	1	1	1	1	1	1
Schlimpert† .....	1	1	1	1	1	1	1	1	1	1
Reinhart† .....	7	6	3	3	1	1	1	1	1	1
Deneke .....	13	3	13	3	1	1	1	1	1	1
Saathoof .....	12	12	12	12	1	1	1	1	1	1
Totals .....	57	38	122	85	34	8	70	57	214	29

\* Includes the 9 cases of Barker, quoted by Osler.

† Reaction with post-mortem blood.

From this table it will be seen that the general theory concerning the association of mesaortitis, aortic insufficiency and aneurism, and the relation of these conditions to syphilis is supported. In a total of fifty-

seven cases of aneurism the reaction was positive in 66.6 per cent.; also positive in 69.6 per cent. of 122 cases of aortic insufficiency and in 81.4 per cent. of seventy cases of mesaortitis.

The most striking results are those of Citron, with positive results in 62.6 per cent., Collins and Sachs 77 per cent., Clough 66 per cent., and Swift 50 per cent. in aortic insufficiency; Fraenkel and Much<sup>4</sup> in 83 per cent. of cases of mesaortitis; Collins and Sachs in all of five cases of aortic aneurism, and Donath's 85 per cent. of twenty-seven cases of mesaortitis, aneurism and aortic insufficiency. If doubtful reactions were included some of these percentages would be higher.

On the other hand, it is seen that positive results in valvular lesions other than aortic insufficiency are relatively infrequent, in less than 25 per cent. of those given in the table. Also in arteriosclerosis of the intimal type it occurs infrequently; the largest series, that of Hasenfeld and Szili, giving but 10.6 per cent. in 188 cases.<sup>5</sup>

In view of these results it is evident that a more thorough investigation of this field may lead to a very satisfactory separation of syphilitic from non-syphilitic vascular lesions and therefore to a more rational therapy. The three important conditions described have long been treated by many practitioners as syphilitic affections, this treatment being based on a history of syphilis and the knowledge that as a result improvement was not infrequent. One cannot hope to cure an aortic lesion, but the process, be it aneurism, mesaortitis or insufficiency, may perhaps be arrested or the progress of the disease influenced by vigorous antisyphilitic treatment.

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4. It must be admitted that some doubt has been raised recently concerning the accuracy of results with blood taken at autopsy. Thus Bruck points out the frequency of positive reaction with post-mortem blood from definitely non-luetic individuals. The results of Fraenkel and Much and of Schlimpert must therefore be accepted tentatively. In this connection see Löhlein M.: *Zur Frage der Verwertbarkeit der Wassermannschen Syphilisreaktion an der Leiche*. *Folia serologica*, 1910, iv, 227.

5. In addition to the tabulated cases it may be noted that Lenhartz has recently commented on the frequency of a positive Wassermann in aneurism, early aortic disease and sclerosis of the coronary arteries. Saathoff reports positive results in cases of aneurism and angina pectoris, but gives no figures. Oignard made the test on twenty-five patients with cardiac disease and obtained a positive reaction in all of those suffering from aneurism or uncomplicated aortic insufficiency and negative results in the cases of mitral disease. Sonnenberg reports nine cases of aneurism with aortic insufficiency, in five of which a positive Wassermann was obtained, as it also was in half of sixteen cases of arteriosclerosis in young individuals. McIntosh reports a positive Wassermann in one case of aneurism as do Coenen and Wolfsohn in one each of aortic insufficiency. More recently, Krefling has reported positive results in eight of nine cases of aortic insufficiency.



This view is supported by Longcope and also by Cabot, who states that since the discovery by Wright and Richardson of the spirochete in mesaortitis it has been his practice to "push antisyphilitic treatment in all cases of non-rheumatic cardiac disease in which there is a history of syphilitic infection, especially if the Wassermann reaction is obtained." Such patients, he thinks, respond to this treatment better than would be expected under the ordinary treatment of rest, purgation and cardiac stimulation. Collins and Sachs definitely recommend antisyphilitic medication in cardiovascular conditions giving a positive Wassermann, and state that marked improvement has followed such treatment. Laubry and Parvu report improvement in certain cases of aortic lesions giving a positive Wassermann reaction and placed under antisyphilitic treatment.

There is some evidence that the Wassermann reaction may also lead to the recognition of the syphilitic nature of various vascular conditions not included in the group just discussed, and also of disease of the myocardium. The view that a primary interstitial myocarditis associated with panarteritis may be due to syphilis is held by many writers, and in this country has been emphasized, especially by Adler, who reports very satisfactory results from antisyphilitic treatment. It is not surprising therefore to find that Schlimpert reports a positive Wassermann reaction in two cases and Schütze in one case of coronary sclerosis; Reinhart in three of six cases and Citron in one case of myocarditis. Positive reactions have also been obtained in individuals with sclerosis of the pulmonary artery and cerebral aneurism (Schlimpert), and by Clough in one case, and by Laubry and Parvu in three cases of obliterating endarteritis with gangrene, and by the latter also in one of diffuse endarteritis of the extremities.<sup>6</sup>

Much work must be done before definite conclusions can be reached concerning the more obscure vascular lesions. We may hope, however, in view of what has already been accomplished, for results which may be utilized to shape therapeusis.

I have been especially impressed, in studying the statistics of syphilis, by the frequent association of cardiovascular lesions with the so-called parasyphilitic affections of the nervous system and their relative infrequency in syphilis without paralysis. Thus Straub found mesaortitis in sixty-nine of eighty-four paralytics (82.1 per cent.) with syphilis, but.

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6. Kaliski and Buerger have failed to get a positive reaction in sixteen cases of thrombo-angiitis obliterans. This statement is made by Noguchi in reporting two cases of Raynaud's disease with negative reaction.

on the other hand, aortitis was present in only seven of seventy-one syphilitics (9.9 per cent.) without paralysis. It was present in 41 per cent. of the cases of progressive paralysis examined by Chiari and in 63 per cent. of twenty-four cases of tabes described by Müller and Rogge (Strümpell's clinic), and Mönckeberg states that an analysis of the published cases of mesaortitis shows that 44 per cent. are associated with metasyphilitic affections.

Such vascular lesions are, apparently, as truly parasymphilitic as are tabes and progressive paralysis; and this view, suggested by pathological studies, is supported by the results of the Wassermann reaction. One wonders whether the individuals with parasymphilitic vascular and nervous lesions are those in which active virus persists, while those without such lesions represent individuals in which the spirochete has been destroyed by proper treatment. If the former, one may advance a second hypothesis, that based on the finding of the spirochete in mesaortitis, to the effect that the nervous lesions may be due to the poison of the spirochete persisting in the chronic vascular lesions.

#### CIRRHOSIS OF THE LIVER

Aside from affections of the cardiovascular system, the only disease of interest to the internist concerning which we have much data is cirrhosis of the liver. Of the reports<sup>7</sup> which I have been able to collect, twenty-two of thirty cases have given a positive Wassermann reaction. Of these, about half were in individuals with a history of syphilis; in the others, a history of antecedent syphilis was absent or doubtful. Of special interest is the negative result in a case of Banti's cirrhosis (Pick and Proskauer), a lesion which has been considered as possibly syphilitic. Esmein and Parvu report a positive reaction in a case of cirrhosis with hypertrophy; under mercurial treatment rapid improvement was noted. Clough found five alcoholic cirrhoses negative and one, clinically syphilitic, positive. It is possible, therefore, that further work may show that the etiology of various cirrhoses may be determined by this method, thus adding to our knowledge of the pathology of the liver and aiding in the establishment of a satisfactory treatment. It is also possible that the ascitic fluid of cirrhosis may be utilized for the test, as demonstrated by Esmein and Parvu, by Swift and by Cheney.

7. Citron, 2 cases; Hoehne, 2; Fraenkel and Much, 2; Ballner and Muscatello, 1; Noguchi, 7; Esmein and Parvu, 1; Pick and Proskauer, 1; Clough, 6; Swift, 7; Cheney, 1.

## SURGERY

Among the first to recognize the importance of the Wassermann reaction in the practice of surgery were Karewski and Coenen. Karewski, early in 1908, emphasized the value of the method in the differential diagnosis of gumma and tumor, of tuberculous and syphilitic affections of bone, and as an additional means of establishing the diagnosis in those cases in which, although the presence of syphilis is probable, an absolute diagnosis could not otherwise be made. On the basis of his experience with twenty-eight tests, he emphasizes the value of the reaction in the recognition of syphilis of bone and in the determination of treatment, and comments on the advisability of replacing the therapeutic test by the serum reaction.

Coenen, later in the same year, published the results of seventy observations. His cases include a great variety of surgical affections which may be grouped in three classes, diseases of bones and joints, tumors and diseases of blood-vessels. Of the seventy individuals tested, thirty presented clinical evidence of syphilis and twenty-six gave a positive Wassermann reaction. Of these latter, mainly individuals with disease of bone, a history of syphilis was lacking in nine. Coenen also emphasizes the importance of the reaction in the differentiation of syphilitic bone disease from tumors, especially sarcoma. He points out the difficulty of making a histological diagnosis between an inflammatory condition of bone, syphilis and sarcoma on the small piece of tissue removed at operation and hastily examined. The Wassermann reaction under many circumstances may therefore be preferable to a histological examination. He also considers it important in the diagnosis between syphilitic leukoplakia and early cancer of the tongue. Here, however, one must interpret with caution, for cancer frequently develops in the lesion of leukoplakia.

Baetzner, after a study of 120 cases, urges the use of the reaction in the differentiation between chancre and peculiar localized inflammatory conditions and between gummata and necrotic tumor-like masses, a positive reaction assuring early treatment. He has also found it of assistance in joint and bone disease. He concludes that the method ranks in importance with those of histology, bacteriology and radiography in the diagnosis of syphilitic disease. Pick and Proskauer likewise emphasize the importance of the method in certain lesions, as sarcoma, infectious granuloma and chronic inflammation, which are not readily differentiated from syphilis by histological examination.

Clough refers to two patients with tumors of the chest wall clinically resembling sarcoma. Each gave a positive Wassermann and on exploratory excision and histological examination evidence of lues was found.

Swift, who has obtained positive results in three of four cases of gumma of the testicle, makes an interesting observation on this subject. In one patient a testicle was removed because of a diagnosis of tuberculosis; subsequently the other testicle became involved. A positive Wassermann reaction at this time led to antisyphilitic treatment and marked improvement.

Several references to the use of the reaction in the recognition of syphilitic strictures of the rectum are also at hand (Wolfsohn, Clough), and Wolfsohn, who details some observations on its use in surgery, classes it with the tuberculin reaction in importance.

Several observers (Citron, Reinhart, Noguchi, Clough) have obtained positive reactions in chronic bone and joint disease, as chronic arthritis and spondylitis. Donath and Heckman have called special attention to these conditions. In Donath's twenty-seven cases of vascular disease, of which 88 per cent. gave a positive reaction, polyarthritis occurred in three. Although these cases all gave a history of articular rheumatism, he believes that certain special features of the joint affection show the lesion to be of a syphilitic nature rather than a true rheumatic polyarthritis.

Swift also emphasizes the value of the test in disease of bone; he has obtained sixteen positive results in seventeen cases of osteomyelitis, periostitis, and gumma of bone. Four of these were confirmed by *x*-ray and all improved under treatment with potassium iodid.

Heckman gives a detailed study of four cases of arthritis deformans of the mono-articular type and eleven of the polyarticular type. A fairly definite history of syphilis was obtained in all of the first group, without evidence of tertiary lesions, and all of these gave a positive Wassermann reaction. In six of the second group (polyarticular type), definite evidence of syphilis was present and less definite evidence in one. In seven cases the Wassermann reaction was definitely positive and in four weak or doubtful. On this evidence of the frequently positive Wassermann reaction, the fairly constant history of syphilis, and the improvement under antisyphilitic treatment, Heckman comes to the conclusion that not only the mono-articular, but also to a large degree the polyarticular form of arthritis deformans, has a luetic basis. Swift reports positive results in two cases of mono-articular and one of polyarticular chronic arthritis, with cure under antiluetic treatment.

It is evident from this summary that in surgery the Wassermann method for the diagnosis of syphilis is at least of equal importance with the tuberculin reaction. Although, as Baetzner points out, a positive reac-

tion is an indication of general disease and not of local lesion, nevertheless, with a doubtful local lesion, a positive reaction supplementing other methods of examination, is of great value. The reaction has not thus far been extensively employed in surgery, but if the reported results are confirmed we may confidently expect it to become one of the common procedures of the surgical clinic.

#### LARYNGOLOGY

Specialists treating the throat, nose and ear have utilized the Wassermann reaction in the diagnosis of obscure ulcerative lesions, in the study of ozena and for the purpose of determining the relation of syphilis to certain forms of deafness.

Ozena, on account of its frequent association with congenital syphilis, has been especially studied. It has long been a disputed point as to what percentage of cases of ozena was to be ascribed to syphilis. Investigations to determine this point by demonstrating the presence of the spirochete have been uniformly unsuccessful, and it is but natural that the assistance of the Wassermann method should be invoked. Alexander has examined twenty-six cases of ozena, free of clinical evidence of syphilis, with negative results in all, but takes the stand that a negative reaction is of no value and does not exclude the syphilitic origin of the disease.

Sobernheim obtained similar results in seventeen cases and concludes, in the light of the frequently positive Wassermann in tertiary and latent syphilis and in tabes and general paralysis, that ozena is not necessarily a metasymphilitic disease. In a later communication he reports a positive reaction in two cases of ozena with evidence of syphilis.

Scheier reports negative results in eight cases of simple ozena and a positive result in one case in an individual with tertiary syphilis. Negative results have also been reported by Weinstein, who examined eight cases.<sup>8</sup> Eisenlohr, one of the first investigators in this field, also obtained negative results in fifteen cases. It is as yet a little difficult to decide as to the exact importance of these negative results. It is certain that a negative Wassermann reaction is uncommon, as a constant result, in any large series of cases representing acquired, inherited or latent syphilis. The conclusion, therefore, seems justified that ozena may occur independently of syphilis.

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8. These cases are reported from Scheier's clinic and apparently are the same observations presented above under Scheier's name in the discussion of Sobernheim's work.

Sobernheim has also called attention to the value of the Wassermann reaction in the differential diagnosis of Vincent's angina and of early syphilitic ulceration of the tonsil, a negative as well as a positive reaction being of aid both in diagnosis and treatment.

Weinstein called especial attention to the importance of the reaction in the differential diagnosis between syphilis and tuberculosis of the respiratory mucous membranes, both as an adjunct to the histological examination of excised tissue and as a substitute for the therapeutic test. He gives instances in which a positive serum reaction led to the clearing up of a diagnosis which lay between syphilis and tuberculosis, but which could not be determined by history, clinical appearance, histology or bacteriology. In all the cases in which the diagnosis of syphilis was established by the serum reaction, appropriate treatment led to rapid improvement.

Weinstein also speaks of the use of this method in connection with the diagnosis of primary syphilitic lesions of the mouth, of leukoplakia, and in the differential diagnosis of Vincent's angina. While a negative result should be considered cautiously, he believes it strong evidence against syphilis.

My own experience has been such as to indicate that the Wassermann reaction promises to be of great value in the diagnosis of affections of the respiratory passages.

The following experience is illustrative. A laryngologist sent me a small piece of tissue from an extensive ulcerative lesion of the post-pharynx, with a request for histological examination. He was inclined to a diagnosis of syphilis, but as one of the two dermatologists who were consulted concerning an associated lesion of the skin had made a diagnosis of tuberculosis and the other of syphilis, he was in doubt. On examining the sections, I could not make a diagnosis between syphilis and tuberculosis, and in this found myself in agreement with three other pathologists. The serum test was tried, and a strongly positive reaction was taken as definite evidence of syphilis and appropriate treatment instituted.

I have been able to find only one reference to the use of the Wassermann reaction in the study of diseases of the ear. Busch has examined twenty-nine cases of nervous deafness and seventeen of otosclerosis. Positive reactions were obtained in 52 per cent. of the former and in 23.5 per cent. of the latter. He concludes that the method is of value in establishing the proper treatment of these conditions and suggests that it also

may be of value in clearing up the etiology of some of the as yet little understood chronic affections of the ear.

#### OPHTHALMOLOGY

Leber appears to have been the first to use the Wassermann reaction in the diagnosis of diseases of the eye. In a series of 160 examinations he found sixteen certainly syphilitic affections, in 93.7 per cent. of which a positive reaction was obtained, and ninety-five doubtful cases with a positive serum test in 42.1 per cent. He emphasizes the importance of the test, not only for diagnosis and treatment, but also as a means of establishing more exactly the etiology of many diseases of the eye. In this connection, he states that a positive reaction was obtained in 53.9 per cent. of thirty-one cases of keratitis, exclusive of the suppurative form, in iritis in 33 per cent., in retinitis and chorioiditis in 26 per cent., and, finally, in eye lesions accompanied by cerebral symptoms in 59.3 per cent. He especially refers to the importance of the test in the differentiation of tuberculous and syphilitic disease.

Gutmann comments on the value of the Wassermann for early diagnosis and early treatment, for the differential diagnosis of tuberculosis and tumor from syphilitic disease, as a substitute for the removal of pieces of tissue for diagnosis, and for the recognition of the cause of muscle paralysis. He quotes cases illustrating early diagnosis in which patients were successfully treated by mercury who, ordinarily, would have been operated on.

Cohen has examined sixty-four cases; positive reactions being obtained in cases of iritis, keratitis, chorioiditis, cataract, optic atrophy, optic neuritis, and muscle paralysis, in 61 per cent. of known syphilis and in 29 per cent. of suspected or doubtful syphilis. Cohen concludes that a negative reaction is of some diagnostic aid and a positive reaction of direct value both in diagnosis and treatment.

Schumacher reports 215 examinations, with positive results in 40 of 58 cases of syphilis and in 24 of 13 cases of suspected syphilis, his positive results occurring in much the same group of cases as those reported by Cohen, and he supports the latter in the belief that a negative reaction in ophthalmic cases is of considerable diagnostic value. In the doubtful cases he considers the reaction to be of the greatest value, although in hereditary syphilis free from recent acute symptoms a positive reaction is rare. He presents observations concerning the development of tuberculosis secondary to changes due to syphilis in the internal eye, such cases giving both the Wassermann and tuberculin reactions, and for this

reason recommends the tuberculin treatment as well as anti-syphilitic treatment.

Best has made observations which lead him to think that the Wassermann reaction may be useful in distinguishing between hereditary syphilitic chorioidoretinitis and clinically similar forms of non-syphilitic origin.

Other studies are those of keratitis by Hoehne, Pisani and Silbersiepe. Pisani obtained positive results in all of seven cases of parenchymatous keratitis, and regards these results as definitely establishing the syphilitic nature of the disease.

Silbersiepe has examined 100 cases of keratitis parenchymatosa with the aid of the Wassermann reaction, and finds that it supports the theory of the great importance of syphilis, especially hereditary syphilis, in the etiology of the disease.

Noguchi gives a table of twenty-nine cases of eye diseases, in fourteen of which a positive Wassermann reaction was obtained; in eight of twelve cases of interstitial keratitis, four of six cases of iritis, one of optic neuritis, and in one of two cases of acromegaly with ocular symptoms. Negative results were obtained in optic atrophy (five), scleritis, chorioiditis, and paralysis of the external rectus. Swift has obtained positive results in uveitis, central amaurosis and optic atrophy.

#### DERMATOLOGY

The use of the reaction as an aid in the diagnosis of the common skin lesions of syphilis need not be discussed. Its use in this field has been definitely established. Of other diseases of the skin of doubtful etiology, one that has been especially investigated is scleroderma. Castelli reports positive results in two, Noguchi in one of four and Whitehouse in four of five cases. Whitehouse's investigation was suggested by a positive result obtained by Lustgarten. His cases were those of diffuse scleroderma: three gave a strong and one a faint positive reaction, and one was negative. The two latter patients had been under anti-syphilitic treatment, one for over a year and the other for six months. In addition to these five cases of the diffuse type, two cases of the band-like morphea type gave negative reactions. Whitehouse considers it not improbable, in view of the histological resemblance between the changes in scleroderma and syphilis, that syphilis may be an etiological factor in the diffuse form of scleroderma. Swift,<sup>9</sup> however, has examined three cases of sclerodactylia and one of the diffuse form with negative results.

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9. Personal communication.



Another condition especially studied is leukoplakia of the tongue. The status of leukoplakia has never been quite clear. That it may occur independently of syphilis is known. But its frequency in well-defined syphilis renders doubtful the diagnosis when leukoplakia occurs in the absence of other symptoms of syphilis, that is, in those conditions in which it is the only manifestation of an otherwise latent syphilis. Under such circumstances the question of treatment is doubtful and for that reason the help of the Wassermann reaction has been invoked. Pürckhauer has examined twelve cases, with positive results in ten. Positive results have also been reported by Coenen in three cases, by Schlimpert in seven of ten cases, by Swift in six of seven cases and by Joseph. It would seem that, as a rule, leukoplakia is to be regarded as evidence of syphilis and often the only manifestation of a latent syphilis. If so regarded and treated as such, it is possible that cancer of the tongue, of which leukoplakia is frequently a forerunner, may in many instances be prevented.

Neisser has emphasized the importance of the reaction in the differentiation between lupus and tertiary syphilis and between early round-celled sarcoma and chancre. He presents illustrative cases, one of which had been wrongly diagnosed as lupus of the nose and treated as such, with the result that extensive destruction of the nose, pharynx, gums and both eyes resulted. A positive Wassermann reaction led to anti-syphilitic treatment and improvement, but too late to save the eyes and prevent extreme disfiguration of the face.

The literature contains numerous reports of isolated instances in which the Wassermann reaction has led to the recognition of the syphilitic nature of ulcerative lesions at first supposed to be tuberculous (Clough). In all such cases improvement has followed anti-syphilitic treatment. Another use of the Wassermann reaction, as pointed out by Swift, is in those cases in which a syphilitic roseola is marked by other eruptions, as for example, scabies.

#### GYNECOLOGY, OBSTETRICS, AND COLLES' LAW

The Wassermann reaction in gynecology is in part a matter of diagnosis, but to a greater extent—and this is particularly true of its relation to obstetrics—it is of importance in the interpretation of those general principles embraced under Colles' and Profeta's laws. The significance of the results obtained concerning this latter aspect of the problem overshadow the use of the method in the diagnosis of local lesions. The

results may be said to render necessary a revision of Colles' and Profeta's laws and to constitute practically a new biological law.

One of the first investigators in this field was Opitz, who concluded that the reaction merited the earnest consideration of the gynecologist and obstetrician. It became at once not only a means of recognizing syphilis in women and the new-born in which the diagnosis was doubtful, but also a means of clearing up the etiology of stillbirths and habitual abortion. Such observations (Knöpfelmacher and Lehdorf, Bauer, Bab, Ledermann) led to a thorough investigation, with the aid of the reaction, of the principles embraced in the laws of Colles and Profeta.

It may perhaps be unnecessary to observe that Colles' law covers those instances in which the mother of a syphilitic child is herself immune to infection and cannot be infected, even though she presents no signs of the disease. It has always been a question whether the immunity is real or whether the mother is so lightly infected as to present none of the actual manifestations of the disease. Profeta's law refers to the reverse condition, that in which an apparently healthy child, born of a mother suffering from active syphilis, can suckle its mother without contracting the disease from her. Here again the question is that of immunity versus latent infection.

The Wassermann reaction has been used to determine whether in the first instance the mother and in the second the child actually has syphilis, or, on the other hand, is really immune to the disease. The use of the test for this purpose is based on the assumption that a positive Wassermann reaction means active syphilis, if not, indeed, the actual presence of the spirochete. All recent work, especially that with latent acquired syphilis, indicates that this assumption is correct. Positive reactions in the mothers of syphilitic children and in the apparently healthy children of syphilitic mothers have therefore been considered as evidence of actual syphilis in each instance, thus removing any interpretation of Colles' or Profeta's law based on the principles of immunity. The results all hold together. Thus Knöpfelmacher and Lehdorf obtained a positive reaction in 56 per cent. of thirty-two women apparently healthy, but mothers of syphilitic children; Buer obtained similar results in all his cases, as did also Ledermann and Engelman and Bergmann. Such results in small groups of cases led to the conclusion that these apparently healthy mothers were really affected with latent syphilis, and led to numerous other investigations (Bunzel, Reinhart, Frankl), one of the most extensive of which, that of Baisch, may be quoted in detail. It includes a study of 140 cases, with a search for spirochetes in the fetus and pla-

centa and the use of the Wassermann method on the mother. Of these, 102 were mothers with positive Wassermann reaction whose children had syphilis, evident macroscopically, or shown by the finding of the spirochete in the tissues. Seventy-five of these mothers were without clinical evidence of syphilis. On the basis of finding spirochetes (Trinchese) in the spaces between the villi in the maternal portion of the placenta in selected cases Baiseh concludes that the spirochetes are present in the blood of the mother and that therefore the positive Wassermann reaction is not an evidence of immunity of the mother, but rather of latent syphilis, or, as he puts it, the mother is refractory to infection with syphilis because she is already infected. He further shows that in twelve mothers giving a negative reaction, spirochetes were present in the maternal portion of the placenta, thus indicating that all such mothers are syphilitic and that there are no exceptions to the principle of Colles' law. As to Profeta's law, much the same conclusion has been reached. The children of syphilitic mothers are not immune to syphilis but are either syphilitic, that is, have latent syphilis, or are healthy, and in the latter case may later become infected.

Aside from the light thrown on the problems of congenital syphilis,<sup>10</sup> the demonstration of latent syphilis under these circumstances is of great importance in that it points to the necessity of treatment, in order that active manifestations of the disease may be prevented.

Frankl, who has studied in detail eighty-seven cases, states that a woman who has given birth to a syphilitic child and has a positive Wasserman reaction is to be considered as having latent syphilis and should be given specific treatment without waiting for further manifestations of the disease. Also a positive reaction in the child of a syphilitic mother, though the child be apparently healthy, demands specific treatment for the child. McDonagh urges that all apparently healthy pregnant women giving a positive reaction should receive specific treatment through the entire pregnancy, for, as the result of such treatment, women habitually aborting may have healthy children.

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10. The reaction has added little of special interest to the diagnostic methods of the gynecologist, though some casuistic reports are of interest, as in the case of Neisser, in which the uterus was extirpated for what appeared on histological examination to be a round-celled sarcoma of the cervix. The later development of the secondary lesions of syphilis and a positive Wassermann indicated the lesion to be a chancre, from which experience was drawn the lesson that if the serum diagnosis had been attempted first the operation might have been avoided. It is also worthy of note that Bunzel found six of seven cases of eclampsia positive at the height of the disease, but negative after the disappearance of the symptoms. Under such conditions, therefore, the reaction is to be considered with caution.

A closely analogous investigation is that of wet-nurses. Physicians have long sought to rule out two infections, tuberculosis and syphilis, without, however, in the latter having any definite criterion in the absence of symptoms. Bergmann has examined seventy-five wet-nurses, only two of whom presented evidence of syphilis, and found a positive Wassermann reaction in seven (9.3 per cent.). Rietschel found a positive reaction in 10 per cent. of the wet-nurses whom he examined. Both Bergmann and Pust state emphatically that every physician or clinic seeking a wet-nurse should have a Wassermann reaction done, irrespective of clinical findings. This statement is supported by Bruck and is in accord with the observations of Opitz and Rietschel.

#### LATENT SYPHILIS

It has been seen that the study of the principles of Colles' law has furnished valuable evidence in support of the theory of latent syphilis. Of the greatest importance, however, in this regard, as well as from the point of view of public health, are the results of the use of the Wassermann reaction on the prostitutes of foreign cities. Such investigations have been made by Beckers, Hoehne, Jundell, Almkvist and Sandman, and by Dreyer and Meirowsky. Beckers examined eighty prostitutes, of whom thirty-three, or 41.25 per cent., gave a positive reaction and five, or 6.25 per cent., a doubtful reaction. Of those reacting positively only eleven, or one-third, presented clinical evidence of syphilis. Of fifty who had had syphilis but presented no symptoms twenty, or 40 per cent., gave positive reactions. Jundell and his associates obtained 23 per cent. of positive results in thirty-two prostitutes without clinical evidence of syphilis. Hoehne examined 107 *puella publica* with no manifest syphilis, and obtained a positive reaction in 21.5 per cent.

The investigation of 100 women by Dreyer and Meirowsky is most complete. They found two with active syphilis and fifty-five with a history of syphilis and earlier treatment but no manifestations. Of these fifty-seven, thirty-nine, or 68.4 per cent., gave a positive reaction. In the remaining forty-three with no history or manifest lesions of syphilis, a positive reaction was obtained in twenty-six, or 60.5 per cent. It is seen, therefore, that if the cases with a positive Wassermann reaction only are added to those with a history of syphilis, or with the lesions of the disease, we have 83 per cent.<sup>11</sup> of 100 women presenting evidence of

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11. The figures given are those obtained by the original Wassermann method. The investigators used also Stern's modification, and by this means obtained a somewhat higher number of positive reactions, that is, 78 per cent. for the first group, 74.4 for the second group, and 89 per cent. for the combined groups.

infection. Or, to put it another way, we have 2 per cent. with active lesions and 81 per cent. with either a history of syphilis or a positive Wassermann reaction as evidence of the frequency of infection in this class. Moreover, of those giving a negative reaction all but three had been registered less than a year and none for more than three years. Few, therefore, would appear to escape: all apparently become infected within three or four years of exposure. Syphilis occurred in those between 21 and 25 years of age in thirty-four of the total number as compared with seven of the same period free of the disease. In the next age period of 25 or 30, thirty-one were infected, as compared with two free of syphilis. Of the total of 100, only one of twenty-four women over 30 years of age was non-syphilitic. These figures, if we accept the Wassermann reaction as evidence of active syphilis, would appear to throw grave doubt on the possibility of a natural immunity to syphilis.

When one considers that in the past the presence of syphilis could be demonstrated by history and examination in only about 50 per cent.<sup>12</sup> of these women, the value of the Wassermann method as presumptive evidence of syphilis becomes apparent. It is evident that in European cities, in which cases of this class are registered and carefully watched, many problems of syphilis may be studied: as (1) the question of the infectivity of individuals with a positive Wassermann reaction as the only symptom of the disease; (2) the control of this mode of infection; (3) the study of the frequency of the development of tertiary and quaternary lesions in individuals presenting only a positive Wassermann reaction; (4) the influence of treatment on the Wassermann reaction, and (5) other general problems concerning individuals who are, essentially, spirochete-carriers without evidence of disease.

#### SPECIAL APPLICATION OF THE REACTION

The experience with prostitutes, wet-nurses, and especially the information brought out by the study of the laws of Colles and Profeta have thrown an interesting light on the question of so-called latent syphilis, or, as it is now frequently termed, "syphilis without manifestations." Many authors are of the opinion that in so-called latent syphilis we have to do with visceral syphilis giving no outward (clinical) manifestations of disease and recognizable only by a positive Wassermann reaction. If this can be substantiated—and this is a view already supported by many investigators—and if we are to regard a positive Wassermann reaction as

12. Bruhns and Lumme's statistics give 3,179 as treated for syphilis and 3,118 as not treated for syphilis. The figures are for fifteen years (1892 to 1907).

evidence of active syphilis, the reaction has many other practical applications which are suggested by what has been said in the discussion of Colles' law, of wet-nurses, and of prostitutes. One of these is the use of the test in the examination of applicants for life-insurance. Ledermann has suggested that it would be of value in those cases in which the examiner suspects syphilis but cannot establish a diagnosis by history or symptoms. This is of particular interest in view of the fact that the vital statistics of all life-insurance companies indicate that individuals with syphilis are not as good risks as those who are non-syphilitic. Recently Brockbank, who has investigated the subject most thoroughly, made the statement that "no syphilitic proposer who cannot bring forward satisfactory evidence of having undergone proper treatment should be accepted." The difficulty naturally is to decide on what is "satisfactory treatment." Swift prophesies that for this the Wassermann method will eventually be the test, and that the evidence required will be repeated negative reactions over a period of time sufficient to show that the individual is free from the disease. He also believes that a positive reaction, even when clinical symptoms are absent, should be considered as sufficient evidence for rejection or for acceptance at an advanced premium. McDonagh holds that a candidate giving a positive reaction, even though years have elapsed since the original infection, should be considered ineligible on the ground that the positive reaction is an indication of a visceral lesion which will ultimately shorten life. On the other hand, he recommends the acceptance of a candidate who after two years of treatment gives a negative reaction after intervals of three, six and nine months. Certainly, if we are to accept a positive Wassermann reaction as a sign of active syphilis and also accept Brockbank's rule that "no proposer showing signs of the disease in any one of its stages should be accepted," these conclusions are logical.

Another question is that of marriage. The infectious stage of syphilis is generally considered to be three or four years. If *lues ignorata* is as common as the Wassermann reaction in the hands of Dreyer and Meirowsky indicates, and if those without manifest lesions but with a positive Wassermann are truly spirochete-carriers, whether treated or not, our views concerning the control of those exposed to syphilis must be altered. It seems probable that the reaction will be an aid in deciding the question of marriage, and that to the rule which demands thorough treatment and a lapse of years will be added successive negative Wassermann reactions.

Also it may be used to set at rest the mind of the syphilophobic by convincing him after the repeated negative tests of the non-existence of the disease: in those instances in which the disease really is present a positive reaction allows proper treatment to be instituted before symptoms appear and the fears of the patient are allayed by assurances of a satisfactory outcome. Bruck has especially emphasized the value of the reaction in syphilophobia and Marcus has used it for this purpose with satisfactory results in two cases.

On the other hand, it is of decided value in those instances in which a patient with a doubtful lesion denies, intentionally or otherwise, the possibility of infection.

Finally, it would appear that the Wassermann reaction will eventually replace the therapeutic test. The latter has frequently been of doubtful value, for it is well known that many neoplasms as well as chronic inflammatory and proliferative conditions improve for a time under iodids. If further work supports our provisional view of the accuracy of the serum test we have a more certain means of diagnosis. A negative reaction will save much valuable time which may be applied to other methods of diagnosis and treatment, while a positive reaction will allow thorough treatment and perhaps not infrequently prevent operative interference.<sup>13</sup>

#### EFFECT OF TREATMENT

Finally, we have the question of the effect of treatment on the reaction and the correlated problem of whether the disappearance of the reaction is to be considered as an indication of cure.

Practically all observers have found that positive results are more frequent in untreated than in treated individuals. In Clow's statistics these two groups are represented by 81 and 65 per cent. respectively; in Bruck's by 82 and 29 per cent. So also in cases which have been carefully followed, it is seen that the number of positive reactions diminishes with the lapse of time and bears also a definite relation to the number of courses of treatment. This is best shown in the table of Jesionek and Meirowsky, illustrating the treatment of latent syphilis:

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13. Many other phases of the work with the Wassermann reaction might be discussed, as its use by the pathologist to demonstrate the origin, syphilitic or otherwise, of various chronic lesions, as for example, fibrous orchitis (Reinhart, Fraenkel and Much, Schlimpert). Also the positive reactions which have been obtained in myxedema (Castelli), infantilism (Pi-ani), and gigantism (Pi-ani), and various other conditions of disturbed nutrition are of interest. Much work must be done, however, before any definite conclusion can be reached concerning the significance of occasional positive reactions in these conditions.

Number of courses.....	0	1	2	3	4 and 5	6 and 7	8 or more
Number of cases.....	76	85	76	55	76	38	16
Per cent. positive.....	97	64	75	47	42	34	31

Swift states that he obtained positive reactions in 74 per cent. of cases treated six months or less, with a steady fall to 31 per cent. in those treated three years. Blaschko, who has examined his cases repeatedly during treatment, finds a gradual disappearance of the reaction in seventy-six of ninety cases. Boas, who has shown very clearly the effect of treatment in causing a disappearance of the reaction, points out that in the late stages of the disease relapses are usually preceded by a return of the positive reaction,<sup>14</sup> and that it is possible by treatment at such times to prevent the return of clinical manifestations of the disease.

Lesser, who has studied 525 cases with the Wassermann reaction from the point of view of ultimate cure, finds 49 per cent. of properly treated cases negative on repeated examination. Even a single course of treatment greatly reduced the positive results, and the percentage of negative results increased constantly with the number of courses of treatment. Contrary to the experience of Jesionek and Meirowsky, he finds the maximum number of negative reactions, 55 to 65 per cent., to occur after four courses. After this the percentage is not increased. He believes that a positive reaction indicates the presence of active spirochetes and that the Wassermann reaction is a reliable index for treatment both as to dose and length of course. Repeatedly negative reactions in later stages indicate the probability of a final cure, but he lays little stress on negative tests early in the disease. He places the period of cure, as indicated by repeated negative tests, at not less than five years, and considers the peace of mind that comes with repeated negative reactions as one of the greatest benefits of the reaction. Butler recommends that a serum test should be made every three months in the early period and every six months in the late period of chronic intermittent treatment. Such a precaution will, he believes, prevent many of the serious and fatal consequences of syphilis.

Much might be added to this discussion of treatment, but it must be sufficiently evident from what has been said that the reaction promises to be a most satisfactory guide to treatment in all its aspects.

14. Donath has described what he calls "provocatory treatment:" that is, in persons with syphilis but a negative Wassermann the administration of mercury causes the reaction to become positive. Donath compares it to the influence of quinin on a latent malaria. The observation has not been generally confirmed and its significance is not clear.



Seldom has a new method, either of diagnosis or treatment, promised as much as does the Wassermann reaction, and if future work tends to the fulfilment of this promise, we have in the Wassermann reaction one of the greatest advances in the history of medicine. The knowledge which it yields, coupled with that resulting from the study of the etiology and from experimental inoculation should eventually place syphilis in the group of subjugated diseases—diseases of which the etiology and pathology is known, for which there exist an absolute diagnostic method and a rational specific treatment.

[Since the preparation of this manuscript there has appeared an interesting communication by Delbet on the syphilitic origin of certain malformations. He obtained positive Wassermann reactions in seven children with congenital affections of the nervous system, Little's syndrome or contractures and in a case of cleft palate. In none was clinical evidence of syphilis present. Delbet is convinced that syphilis is responsible for these conditions more frequently than is generally supposed. (Delbet, P.: *La syphilis dysplasique*, Presse médicale, 1910, xviii, 273.)]

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## PECULIAR ELONGATED AND SICKLE-SHAPED RED BLOOD CORPUSCLES IN A CASE OF SEVERE ANEMIA

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This case is reported because of the unusual blood findings, no duplicate of which I have ever seen described. Whether the blood picture represents merely a freakish poikilocytosis or is dependent on some peculiar physical or chemical condition of the blood, or is characteristic of some particular disease, I cannot at present answer. I report some details that may seem non-essential, thinking that if a similar blood condition is found in some other case a comparison of clinical conditions may help in solving the problem.

*History.*—The patient was an intelligent negro of 20, who had been in the United States three months, during which time he was a student in one of the professional schools in Chicago. His former residence had been Grenada, West Indies, where he had been born and brought up, one of a family of four children, all living, and all well with the exception of himself. His mother was living and in good health; his father had died of accident. At the age of 10 the patient had had yaws. This was a common disease in the locality where he lived. The lesions, as he described them, had been pustular, with formation of ulcers and scabs. On healing, scars, many of which he pointed out, were left. Some of the ulcers had been as large as a silver quarter of a dollar. The disease lasted about one year and during this time he had felt somewhat weak and indisposed. Most of the ulcers had been on the legs and the patient himself had thought that this location of the lesions might have been due to the bruises and scratches that were frequently produced as he ran about, a barefoot boy, through the streets and the brush. He was sure he had never had ground-itch, though he said it was not uncommon in Grenada. He had attended school up to the age of 17. Since leaving school, that is, for the past three years, he had felt a disinclination to take exercise. For about a year he had noticed some palpitation and shortness of breath which he had attributed to excessive smoking. There had been times when he thought he was bilious and when the whites of the eyes had been tinged with yellow. At such times he had not had any pain, chill or fever. Three years previously he had had a purulent discharge from the right ear lasting six months. He had had no diarrheas and no hemorrhages at any time. He denied syphilis and gonorrhea. There was never any rheumatism or other joint trouble. On landing in New York in September, 1904, he had a sore on one ankle for which he consulted a physician. Tincture of iodine was applied and in a week the sore had healed, leaving a scar similar to the others on the limbs. For the past five weeks he had been coughing. Two days prior to examination he had "taken cold," his cough had grown worse and he had had a slight chill, followed by fever. It was this cough and fever for which he wished treatment at the hospital, and of which he chiefly complained, though he mentioned also that he felt weak and dizzy, had headache and catarrh of the nose.

*Physical Examination.*—This showed him to be a young man of typical negro facies, with black, curly hair. He was fairly well developed physically and was bright and intelligent. There was a tinge of yellow in the sclerae and the visible mucous membranes were pale. The eyes were normal; the pupils showed prompt reaction to light and in accommodation. The hearing was good; there was no discharge from the ear. The nose showed chronic and acute rhinitis. The tongue was coated, the pharynx slightly reddened; no scars or other lesions were found here. The cervical glands were definitely enlarged, hard and not painful. The axillary, inguinal and epitrochlear glands were also enlarged, some in the axilla being of the size of almonds. Over the chest and abdomen were several good-sized leukodermatous patches, the intervening skin being rather deeply pigmented. The scars to which he had referred were nearly all located on the legs and thighs, some in the former location being as much as 3 cm. in diameter. There were perhaps twenty scars in all. They were rounded or oval, sometimes of irregular contour, the edges clean-cut; some were like tissue paper or thin parchment to the touch and were lighter in color than the surrounding skin. They were strikingly like scars often seen as the result of syphilis. The chest was well formed. There was fair expansion. Numerous râles, mostly of the moist variety, were heard scattered throughout the chest, especially posteriorly. There was a slight relative dullness over the base of either lung behind. The heart was enlarged to the left, the apex impulse being in the sixth interspace one inch to the left of the left mammillary line. There was but a slight increase in the dullness to the right. A soft systolic murmur, not well transmitted in any direction, was heard over the base of the heart. A faint systolic murmur, or perhaps it would be better to call it an impure first tone—was heard at the apex. The heart's action reminded one of a heart under strong stimulation, though no history of ingestion of a stimulant of any kind was obtainable. Basedow's findings were not to be made out. The pulse was of good quality and of fair volume. The abdomen was not distended nor was it tender. Neither spleen nor liver could be palpated. There was no tenderness over the gall-bladder region. The genitalia were normal. The patellar reflexes were sluggish. There was no ataxia and there were no sensory disturbances.

The temperature on admission was 101 F. It varied between 99 and 101 for four days, then gradually subsided, though for the next three weeks it was often found between 99 and 100 F., though with no regularity. The pulse varied from 64 to 104, averaging about 80. There was never any rapid breathing.

*Urine and Sputum.*—The urine was amber in color, specific gravity 1.010 to 1.014, slightly increased in amount 2,000 c.c.—acid, contained a distinct trace of serum-albumin, a few granular and hyaline casts. This represents the average of several examinations. The urine on admission had a trace of bile. December 28, urinary examinations for hemoglobin and hematoporphyrin were made and none found. Tests were made for paramidophenol, but none was found.

No tubercle bacilli were discovered in the sputum.

*Blood Examination.*—The blood-count on Dec. 26, 1904, was: Red corpuscles, 2,570,000; white corpuscles, 40,000; hemoglobin (Dare) 40 per cent, color index, 0.78. December 31 the count was as follows:

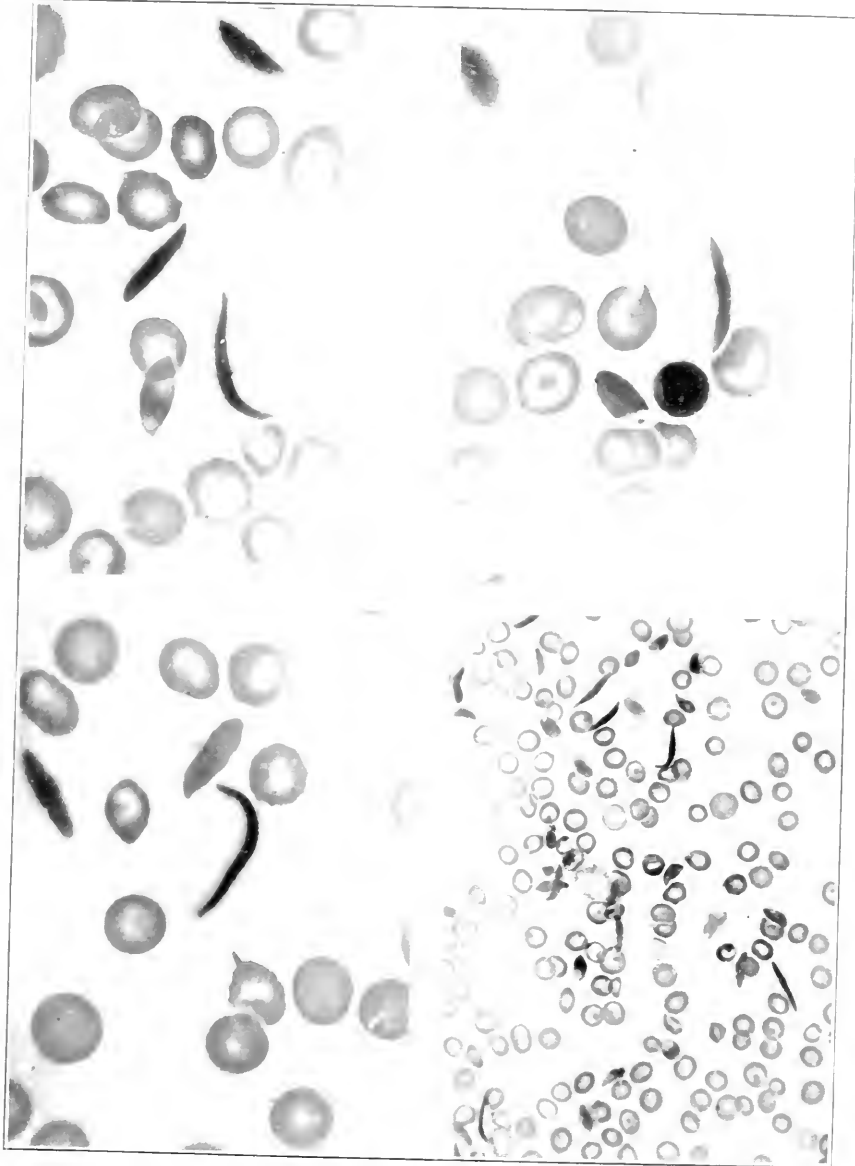
Erythrocytes, 2,880,000.

Leukocytes, 15,250.

Hemoglobin, 50 per cent, (Dare).

The red corpuscles varied much in size, many microcytes being seen and some macrocytes. Polychromatophilia was present. Nucleated reds were numerous, 74 being seen in a count of 200 leukocytes, there being about 5,000 to the c.mm. The shape of the reds was very irregular, but what especially attracted attention





These microphotographs show the peculiar elongated forms of the red corpuscles. Occasional shadow forms are seen with a few nucleated reds. The variations in shape and size are best made out in the low-power figure. The relatively large number of white corpuscles and of normoblasts is not shown by these particular fields.



was the large number of thin, elongated, sickle-shaped and crescent-shaped forms. These were seen in fresh specimens, no matter in what way the blood was spread on the slide and they were seen also in specimens fixed by heat, by alcohol and ether, and stained with the Ehrlich triacid stain as well as with control stains. They were not seen in specimens of blood taken at the same time from other individuals and prepared under exactly similar conditions. They were surely not artefacts, nor were they any form of parasite. In staining reactions they were exactly like their neighbors, the ordinary red corpuscles, though many took the stain heavily. In a few of the elongated forms a nucleus was seen. In the fresh specimen where there was a slight current in the blood before it had become entirely quiet, all of the red corpuscles, the elongated forms as well as those of ordinary form, seemed to be unusually pliable and flexible, bending and twisting in a remarkable manner as they bumped against each other or crowded through a narrow space and seeming almost rubber-like in their elastic resumption of the former shape. One received the impression that the flattened red discs might by reason of unusual pliability be rolled up as it were into a long narrow bundle. Once or twice I saw a corpuscle of ordinary form turn in such a way as to be seen on edge, when its appearance was suggestive of these peculiar forms.

The white corpuscles were made up of polymorphonuclear neutrophils 72 per cent., small mononuclear lymphocytes 15 per cent., large mononuclear forms 7 per cent., polymorphonuclear eosinophils 5 per cent., myelocytes (?) 1 per cent. Many polymorphonuclear cells and some mononuclear forms contained basophilic granules (Neusser's perinuclear basophils (?)). In overheated specimens especially, a number of cells with shadowy outlines and staining but slightly were seen. These resembled white cells.

*Stools.*—The stools were examined not only as a matter of routine, but because of the possibility of detecting the presence of some parasite that might explain the eosinophilia, leukocytosis and anemia, a possibility not at all unlikely in one coming from the tropics and who had lived where ground-itch was a common occurrence. Many stools were thoroughly studied. Considerable mucus was found in some of the stools passed soon after admission, and some of the mucus was blood-stained. No blood was found in the interior of the fecal masses. On two occasions preceding the giving of the thymol, a body was found resembling almost typically the egg of *Ankylostoma duodenale*. Portions of the stools were incubated, but no embryos were to be made out. Thymol was given, but neither eggs nor embryos could be found in the stools, following its administration.

*Treatment and Course of Disease.*—Under treatment, consisting of rest, nourishing food and syrup of the iodid of iron, the fever and râles disappeared, the glands became smaller, the blood improved in quality and the patient left the hospital after a four-weeks' stay, declaring that he felt well. The possible therapeutic influence of the thymol must also not be overlooked. The blood at this time showed 3,900,000 red corpuscles, 15,000 white, 58 per cent. hemoglobin. There was still to be seen a tendency to the peculiar crescent-shape in the red corpuscles though this was by no means so noticeable as before. Nucleated reds were present, though in smaller numbers. Eosinophils were found as before, making up about 5 per cent. of the total number of leukocytes.

We were at a loss to account for this peculiar complexus of symptoms, a condition evidently chronic as revealed by the history of the past three years, with yaws and suppurating otitis as predecessors, yet with acute exacerbations, a condition not clearly explained on the basis of an organic

lesion in any one organ, yet showing cardiac enlargement, albuminuria and cylindruria, general adenopathy, icterus, with a secondary anemia not remarkable for the great reduction in red corpuscles or hemoglobin, but strikingly atypical in the large number of nucleated red corpuscles of the normoblastic type and in the tendency of the erythrocytes to assume a slender sickle-like shape. The leukocytosis with a rather high eosinophil count was also to be noted.

An attempt was made to keep track of the patient, and while he was never afterward under my professional care he was twice seen by myself and several times by Dr. E. E. Irons, whose notes and blood-examinations are here given:

January, 1906: Patient in a hospital for a few days with bronchitis. Rapid recovery.

March 7, 1906: Patient in bed with fever, bronchitis; feels weak. No diarrhea. Red blood corpuscles 2,700,000, whites 30,500; hemoglobin 55 per cent. Blood shows many elongated erythrocytes, a few microcytes. The elongated and spindle-forms seemed to stain more darkly than the normal round red corpuscles. No parasites were seen. The differential count of the white cells showed polynuclear neutrophils 58, large mononuclear 12, small mononuclear 22, eosinophils 7, myelocytes 1. There were 2,279 normoblasts to the cubic millimeter.

A count on March 14, 1906, showed an increase in the reds, a lessening of the whites, but was in other respects practically the same. The stool was normal in appearance, formed, yellowish brown, and no blood or eggs were found. The urine was acid, clear, with no blood or abnormal pigment. There was a trace of albumin, and several granular and hyaline casts were found.

In May, 1906, the patient was seen by Dr. Irons, who found him with some fluid in the left knee-joint; the temperature was 100. Gonorrhea was denied. The patient ascribed the joint trouble to a wrench of the knee a few days before. He recovered after ten days of rest in bed.

In April, 1907, the young man reported that he had been laid up in a hospital from Dec. 26, 1906, to Feb. 26, 1907, with what he called muscular rheumatism. His illness had begun with malaise, pain in the back, the muscles of the legs and arms. He had had a slight fever and was pale. A few days before this illness he had suffered from one of his "bilious" attacks, in which he had had quite severe epigastric pain, had vomited and had later noticed that the urine was dark and that the sclerae were yellowish, though he was inclined to think the icteric hue had been present before the onset of the pain. He was still, he said, somewhat short of breath, but in other respects felt quite well. Since then I have never seen or heard from him.

#### COMMENT

No conclusions can be drawn from this case. Not even a definite diagnosis can be made. Syphilis is suggested by many of the facts, such as

adenopathy and the condition of the heart and kidneys: it might explain the anemia, the arthritis and perhaps also the temperature, cough and attacks of pain resembling hepatic or gall-bladder disease, for as is well known, visceral syphilis may furnish a most bizarre group of symptoms. The Wassermann test was not in use at this time. The scars said to have been due to yaws were like those left by syphilis.

The patient coming from the tropics, one thought of intestinal parasites such as *uncinaria* as a possible explanation of the anemia and the eosinophilia. What were thought to be eggs were found on one occasion only, and after thymol there was temporary improvement.

The odd blood picture made one examine for possible toxic effects of the coal-tar preparations, but neither from the history nor from the examination of the urine was there any evidence that such drugs were habitually taken. We were at this time particularly interested in the subject of chronic acetanilid intoxication as well as in *uncinariasis*, having just had a case of each of these interesting conditions under observation, so that we were on the lookout for such out-of-the-way diseases.

The question of diagnosis must remain an open one unless reports of other similar cases with the same peculiar blood-picture shall clear up this feature.

Schleip, in his "Atlas," pictures fresh unstained preparations of red blood-corpuscles made by his method of diluting the blood 1 to 10 with physiologic salt solution and examining with the aid of the hanging drop chamber. Some of the corpuscles remind one a little of these forms I have described. Yet they are not exactly the same.

Professor Hektoen showed me a specimen that he had encountered in the course of some of his hematologic work, which most nearly resembles these forms. This preparation was one in which washed human corpuscles were suspended in a one-eighth-normal solution of cane-sugar. But neither Dr. Hektoen nor I have been able to reproduce the exact picture again, though using cane sugar solution of the same strength. This, while suggesting that the chemical composition of the fluid suspending the corpuscles may have something to do with these peculiar formations, perhaps suggests more strongly that some unrecognized change in the composition of the corpuscle itself may be the determining factor.

163 State Street.

## THE ELIMINATION OF BACTERIA FROM THE BLOOD THROUGH THE WALL OF THE INTESTINE\*

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It has been recognized for many years that the wall of the gastrointestinal tract forms one of the numerous paths of excretion of foreign substances which have entered the blood. One of the earliest proofs of this vital phenomenon consisted in the injection of antimony subcutaneously, and, after a short interval the demonstration of the presence of this drug in the stomach. Various other drugs and poisons, such as morphin, atropin, strychnin and snake-venom have similarly been proved to pass from the blood through the gastric or intestinal wall, following intravenous or subcutaneous inoculation. In fact this mode of excretion is so well established and so thoroughly accepted that it has led to the routine employment of repeated washing of the stomach and colon in the treatment of poisoning by these drugs. Various other chemical substances, for example, strontium,<sup>1</sup> barium,<sup>2</sup> lithium,<sup>3</sup> manganese<sup>4</sup> and bismuth<sup>5</sup> have been shown to follow, to a greater or less extent, the same excretory route. All these experiments have one essential point in common, namely, that a soluble salt was used for the test, such as lithium citrate, strontium, acetate, or bismuth tartrate. No report has been made of similar tests carried out with insoluble salts.

The experiments reported in this paper do not consider the excretion of salts, but were undertaken to ascertain whether bacteria are excreted from the blood through the intestinal wall. These experiments were sug-

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\* From the Research Laboratory, Department of Health, New York City. Read in abstract before the Society of Experimental Biology and Medicine, Feb. 15, 1910.

1. Mendel, Lafayette, B., and Thacher, H. C.: The Paths of Excretion for Inorganic Compounds, *Am. Jour. Physiol.*, 1904, xi, 5.

2. Mendel, L. B., and Sicker, D. F.: The Excretion of Barium, *Am. Jour. Physiol.*, 1906, xvi, 147.

3. Good, C. A.: An Experimental Study of Lithium, *Am. Jour. Med. Sc.*, 1903, exxv, 273.

4. Harnack, E.: Ueber die Resorption des Mangans, *Arch. f. exper. Path. u. Pharmacol.*, 1901, xlv, 372.

5. Steinfeld, W.: Untersuchungen über die toxischen und therapeutischen Wirkung des Bismuths, *Arch. f. exper. Path. u. Pharmacol.*, 1885, xx, 40.

gested by some previous work which showed the great ease and rapidity with which bacteria are absorbed by the intestinal mucosa. Since this work was undertaken, I have found from a perusal of the literature that this problem is not entirely new, but was considered about twenty-five years ago in relation to the cholera bacillus. Emmerich<sup>6</sup> believed that he could recover his so-called cholera bacillus from the intestine some hours after injecting it into the blood or beneath the skin, and that the bacillus had traversed the intestinal wall. Buchner<sup>7</sup> supported him in this belief. Whatever may have been the facts, the experiments performed to demonstrate this theory were by no means adequate. No care was exercised to exclude the entry into the intestine of the bacilli by way of the bile-duct; indeed, Buchner records that they were cultivated from the liver. So these experiments must be regarded merely as raising the question which forms the nucleus of this paper, but in no way as affording proof of the theorem which Emmerich and Buchner proposed. This is the most serious, but not the only, weak point in these early experiments, which it is unnecessary to dissect any further. It may be added that most of the experiments performed with the soluble salts are open to the same criticism. In this later work, however, other factors, such as the finding of the salt in the stomach or the local lesions of the mucous membranes, render the interpretation of Emmerich and Buchner in most cases justifiable.

In the course of some work carried out on the subject of antiperistalsis in its relation to bacteria,<sup>8</sup> which is the work above referred to, it was found that bacteria which are introduced into the rectum are rapidly absorbed into the blood-current; this may be demonstrated by means of blood cultures, provided sufficient blood be employed for the tests. The question next suggested itself as to whether the reverse is true, whether bacteria can readily be found in the intestine, if they are introduced directly into the blood-stream. Accordingly some preliminary experiments, with this question in view, were undertaken; these were mentioned in the paper on antiperistalsis. It was found that in some instances in which tubercle bacilli were injected intravenously they could be recovered three hours later from the contents of the stomach and of the small intestine; that, in another experiment in which the *Bacillus prodigi*osus

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6. Emmerich, R.: Untersuchungen über die Pilze der Cholera Asiatica. Arch. f. Hyg., 1885, iii, 291.

7. Buchner, H.: Beiträge zur Kenntniss der Neapeler Cholera Bacillen, etc., Arch. f. Hyg., 1885, iii, 361.

8. Hess, A. F.: Antiperistalsis in its Relation to Tubercle Bacilli and other Bacteria in the Intestinal Tract, Jour. Med. Research, 1910, xxii, 129.

was used as a test organism, this bacterium could be regained from the small intestine one hour subsequently. In order to test the possibility of these bacteria having gained access to the intestine by way of the lungs and the upper respiratory tract, two further experiments were conducted. In these the pylorus was ligated preliminary to injecting the bacteria, in order to obstruct effectually this means of entrance into the intestinal tract. In both experiments the *Bacillus prodigiosus* was isolated from the contents of the small intestine. The subject was pursued no further at that time and the question of the path of entry of these bacilli into the lumen of the intestine was left undetermined. It was realized from the work of others that many of the bacilli no doubt were excreted by means of the bile and had reached the intestine by this route. It seemed possible, however, that some might have traversed the intestinal wall. No conclusive data on this point could be found, and accordingly experiments were begun some months later to determine this question.

#### EXPERIMENTS

As elimination by means of the bile of a substance injected into the blood could be presupposed, the first series of experiments necessitated ligation of the common bile-duct. This duct was either doubly ligated, or, in addition, incised just where it enters the wall of the upper duodenum. The operation, performed on rabbits under ether narcosis, was conducted quickly under aseptic precautions, and entailed but slight handling of the intestine. The animals which were subjected to this or to subsequent operations were inoculated as soon as they had recovered from the narcosis; that is, after an interval of one or two hours. The test inoculation was performed after this short interval rather than after the lapse of a longer period, because it was considered that the longer the bile was dammed back after ligation of the bile-duct, the greater was the departure from physiological conditions. Of the three operations in which this procedure was adopted, the *Bacillus prodigiosus* was recovered from the small intestine in two. In the first (Experiment 18), three platinum loops (4 mm. in diameter) of culture were injected and the bacterium was recovered two hours later. It was isolated from the duodenum and the upper ileum but not from the lower ileum. In the second experiment, in which the anatomical conditions were the same, the *Bacillus prodigiosus* was not recovered in the intestine, although it was readily isolated from the gall-bladder. The third test resulted positively. The menstruum used in the various experiments was 0.8 per cent. salt solution; in this last inoculation, however, rabbit serum was substituted.



From these experiments it was evident that, although the bacteria were excreted in the bile, they had gained access to the lumen of the intestine by some other route. Accordingly in the subsequent series of experiments not only was the bile-duct ligated, but the pancreatic duct as well. This duct enters the small intestine about 12 inches below the pylorus, and with this knowledge and a little experience, can readily be found and ligated just before it pierces the intestinal wall. Five experiments of this description were performed, all essentially alike, except for a difference in the quantity of culture material injected, and of the interval which elapsed between the time of injection and the killing of the animal. I shall not detail the manner in which the cultures were obtained from the intestinal contents, as this technic is fully explained in the previous article on antiperistalsis.<sup>8</sup> It is, I believe, sufficient to repeat that the cultures were taken under the strictest precautions to avoid contamination by means of blood; to this end the intestine was seared through all its coats until it had the consistency of parchment, and was then incised by means of a heated scalpel. Of the five experiments in which both the ducts were ligated, all gave a positive result; that is, the test bacillus was recovered to some degree from the small intestine. Of these tests the most exacting were two (Experiments 24 and 25) in which only one loop of culture material was inoculated, and only one hour was allowed to elapse before the animal was killed. For the details the tabulated data may be consulted. It will be seen that the pancreatic duct does not seem to play an important rôle in the excretion of bacteria under the conditions imposed; it seemed a matter of indifference whether or not it was ligated.

The possibility had to be considered as to whether the bacteria, having reached the lungs by way of the blood, had ascended to the pharynx and in this way entered the gastro-intestinal tract. In order to decide this question two experiments were undertaken in which this path of entrance, as well as that by way of the bile-duct or the pancreatic duct, was excluded. To this end the duodenum was divided between ligatures just below the entrance of the bile-duct, and in addition the pancreatic duct was ligated as in the previous experiments. Thus the stomach and upper alimentary tract was severed from almost the entire intestine. The bile still flowed into the upper duodenum, as the duct had not been ligated. This arrangement possessed the advantage of not causing a damming back of the bile, which in all the previous experiments was a factor which existed, and which might be thought to have affected the results. This technic was carried out on three rabbits. The animals recovered one to

two hours after the operation, and were then given an intravenous inoculation of *Bacillus prodigiosus*. The details are recorded in the experimental data (Experiments 26, 27 and 28). They may be summarized by stating that in one instance the result was absolutely negative: that is, the bacillus was not recovered, but that in the two other experiments the *Bacillus prodigiosus* was cultivated from the small intestine below the ligature. The bacilli evidently were not numerous, and they did not seem to be confined to the contents of any one section of the small intestine.

The only possible portal of entry into the intestine in this last series of experiments seemed to be the wall of the intestine itself, as all other paths had been barred. In order to exclude the complicating factor of shock, an experiment was undertaken in which the animal was allowed a longer period of recovery. To this end an intestinal fistula was made in the dog. The operation was kindly performed by Dr. Ernest Sachs, who sutured a loop of the duodenum into the abdominal wall, and in this way made a fistula with a double opening. The upper segment received the stomach contents, the bile and the pancreatic juice. For two days the dog was fed through the fistula and did well, although loss in weight was evident. After this interval the abdominal fistula was closed; this was accomplished by inserting a tube into the opening of the upper as well as into the opening of the lower loop of intestine, and then clamping them off. The physiological condition of the animal from our point of view now resembled that of the rabbits described above, in which the intestine was severed just below the bile duct. The only possible remaining path of communication between the blood-current and the lumen of the intestine was the intestinal wall. An inoculation of four "loops" of *Bacillus prodigiosus*, suspended in .4 c.c. of salt solution, was made into the jugular vein. The dog was chloroformed to death two hours later. As the result of this experiment is given in full detail in a table (Experiment 29), it is unnecessary to do more than to summarize here. The table shows that a large number of cultures were taken from various parts of the intestinal tract, and that from these tubes almost 100 agar plates were made. The *Bacillus prodigiosus* was demonstrated in the duodenum and in the upper and the lower ileum, but not in the cecum or in the large intestine. From the number of negative tests it is evident that the test bacterium was not present in large quantities. This bacillus was isolated also from the urine, and was found in every instance in the gall-bladder. It may be mentioned, in this connection, that almost all my experiments concurred in showing that the bile is the chief factor of

excretion for bacteria given intravenously, and that the urine functionates in this capacity to a less extent.

It seems evident from the various experiments which have been summarized above that in the rabbit and in the dog bacteria are excreted from the blood directly through the intestinal wall. The manner by which this is accomplished, however, appeared by no means clear. Did the bacteria make their way unaided from the vessels through the intestinal mucosa, or were they carried into the lumen by means of phagocytes? As it seemed possible that they were carried through the wall by means of the leukocytes, an attempt was made to demonstrate this phenomenon. To this end, phenolphthalein suspended in water was injected intravenously into rabbits after the bile ducts had been ligated. An attempt was then made to recover this indicator from the intestinal contents. A large number of smear preparations were made from the mucosa of different parts of the intestine, after the contents had been rendered alkaline by means of sodium hydrate. In two such experiments, however, as well as in one in which carmin was used instead of phenolphthalein, no pink or red granules could be seen under the microscope. This fact is perhaps not surprising, considering the moderate degree of permeability which the intestinal wall was found to possess in regard to bacteria. I do not consider this question determined by these few experiments, and leave the question open as to whether bacteria traverse the intestinal wall by a simple passage through the vessels or whether they are carried by means of leukocytes.

#### CONCLUSION

As a result of my experiments it can be stated that bacteria, using the *Bacillus prodigiosus* for the test, are excreted from the blood, not only by way of the liver through the bile, and the kidneys through the urine, but also, to a less extent, directly through the intestinal wall. This was found to take place in one hour when one platinum loop of culture medium was inoculated. In these experiments all other paths of access from the blood to the lumen of the intestine were absolutely closed off, including the path from above by way of the pylorus, and the entry by way of the pancreatic and the bile-ducts. It may be argued that the severity of the operative procedure contributed to the result by rendering the intestinal wall less resistant, and by increasing its permeability. It may be answered that this argument may be brought forward in the case of all experimental data. In the experiments performed, the operations were carried out quickly, and with as little handling of the intestines as possible. Moreover, the question of complicating peritonitis or inflam-

matory reaction did not enter, as, apart from the careful asepsis observed, in almost all cases the animal was killed shortly after.

Although it is a well-recognized fact that bacteria can pass with the lymph-stream through the intact intestinal mucosa, and then migrate from the lumen of the intestine to the blood, the reverse phenomenon, namely, that they pass from the blood through the mucosa into the intestine, has, as far as I am aware, not previously been demonstrated. I do not wish to correlate too strongly this phenomenon, demonstrated in the rabbit and in the dog, with conditions as they exist in man. It is interesting, however, to consider whether the analogy is applicable, whether the wall of the intestine functionates as an excretory organ not only in toxic conditions such as uremia, but also in bacteriemias such as typhoid fever or sepsis, and whether some of the intestinal symptoms and lesions, manifesting themselves in these states, are brought about by what may be termed a mural excretion. This question opens up an interesting field of speculation for the clinician, and a point of view little considered by the pathologist and the physiologist.

NOTE.—Since the above article was written, a short paper has appeared in the *Compt. rend. de la Soc. de biol.* (July 29, 1910, p. 181), entitled "Recherches sur l'Elimination du bacille d'Eberth et des Paratyphiques par l'Intestin," by L. Ribadeau-Dumas et P. Harvier, in which similar experiments are reported. The authors injected typhoid and paratyphoid bacilli intravenously into rabbits, having previously ligated and resected the bile-ducts, and were able to recover the bacilli in the wall of the intestine and in the intestinal canal. The bacilli were cultivated from the appendix, duodenum and from the ileum; more readily in the wall than from the contents of the intestine. The data of the experiments are not given in detail, but the tests seem to have been numerous. The results confirm the conclusions which I have drawn from my experiments.

#### EXPERIMENTAL DATA

##### BACILLUS TUBERCULOSIS INOCULATED INTO RABBIT INTRAVENOUSLY. NO OPERATION

*Experiment 13.*—Weight of animal 1,250 gm.: 130 mg. of a bovine culture suspended in normal salt solution injected into ear vein. Animal pithed after three hours. Positive Inoculations: Blood 3, stomach 2, small intestine 2. Negative Inoculations: Small intestine, 1. Remarks: The blood was caught in a solution of sodium citrate and inoculated intraperitoneally into guinea-pigs. The contents of the intestine were filtered through gauze and allowed to settle before injecting it.

##### BACILLUS PRODIGIOSUS INOCULATED INTO RABBIT INTRAVENOUSLY. NO OPERATION

*Experiment 17.*—Weight of animal 1,800 gm. Three loops of culture material injected. Animal pithed after two hours. Positive Cultures: Duodenum 4, middle ileum 4, lower ileum 1. Negative Cultures: Stomach 4, lower ileum 3.

##### BACILLUS PRODIGIOSUS INOCULATED INTO RABBIT INTRAVENOUSLY. PYLORUS LIGATED

*Experiment 14.*—Weight of animal 2,140 gm. Three loops of culture material in 2 c.c. of salt solution injected: two-hour interval between operation and

inoculation; one hour and three quarters between inoculation and death by chloroform. Positive Cultures: Duodenum, 4. Negative Cultures: Duodenum 6, middle ileum 7, lower ileum 5. Remarks: Of the twenty-two tubes containing 30 c.c. each of bouillon, only four showed *prodigiosus*; 0.5 c.c. of intestinal contents were transferred. The contents of the duodenum were found to be almost sterile.

*Experiment 15.*—Weight of rabbit 1,520 gm. Three loops of culture in 1 c.c. of salt solution inoculated; animal chloroformed two and a half hours after inoculation. Positive Cultures: Duodenum 2, lower ileum 2. Negative Cultures: Duodenum 4, middle ileum 4.

BACILLUS PRODIGIOSUS INOCULATED INTRAVENOUSLY INTO RABBIT. COMMON BILE-DUCT DOUBLY LIGATED AND SEVERED BETWEEN LIGATURES

*Experiment 18.*—Weight of rabbit, 1,850 gm. Three loops of culture inoculated one hour after operation; animal chloroformed to death two hours later. Positive Cultures: Duodenum 3, upper ileum 1. Negative Cultures: Stomach 5, duodenum 7, upper ileum 4, lower ileum 5.

*Experiment 19.*—Weight of rabbit, 2,050 gm. Same amount of material inoculated and same intervals observed as in Experiment 18. Positive Cultures: Bile from gall-bladder. Negative Cultures: Duodenum 6, upper ileum 6, lower ileum 6, stomach 6. Remarks: In this experiment the bile-duct was ligated, but not incised.

*Experiment 20.*—Weight of rabbit 1,900 gm. Two loops of culture suspended in rabbit serum inoculated three hours after operation; same interval as previously between inoculation and killing of animal. Positive Cultures: Upper ileum 3, gall-bladder. Negative Cultures: Stomach 5, duodenum 5, upper ileum 2, lower ileum 5.

BACILLUS PRODIGIOSUS INOCULATED INTRAVENOUSLY INTO RABBIT; DOUBLE LIGATION OF COMMON BILE-DUCT AND PANCREATIC DUCT

*Experiment 21.*—Three loops of culture inoculated into rabbit which was killed three hours later; double ligation of common bile-duct and pancreatic ducts. Positive Cultures: Duodenum, upper ileum. Negative Cultures: Lower ileum. Remarks: Details are missing as regards the number of cultures taken.

*Experiment 22.*—Repetition of previous experiment except that rabbit was killed one and one half hours after inoculation. Positive Cultures: Duodenum, 2. Negative Cultures: Duodenum 4, ileum 6.

*Experiment 23.*—Two loops of culture inoculated. Rabbit killed after two-hour interval. Positive Cultures: Common duct 3, duodenum 2, ileum 3. Negative Cultures: Colon 5, duodenum 3, ileum 2. Remarks: Six loopfuls of the contents of the intestine were used for the transfers to the bouillon tubes.

*Experiment 24.*—One loopful of culture inoculated. Animal killed after interval of one hour. Positive Cultures: Lower duodenum 2, ileum 1. Negative Cultures: Upper duodenum 4, lower duodenum 3, ileum 5.

*Experiment 25.*—This experiment was the counterpart of Experiment 24, except that both ducts were incised as well as ligated. Positive Cultures: Upper duodenum 4. Negative Cultures: Lower duodenum 9, upper duodenum 5. Remarks: For these experiments 0.5 c.c. intestinal contents was transferred to each tube of broth. Agar plates made from these tubes twenty-four hours later showed numerous colonies of *Bacillus prodigiosus*.

CULTURES FROM DUODENUM ABOVE  
FISTULA

Tube No.	Amount of Intestinal Contents Used.	Result. Colonies.
1	1 loop	N
2	3 loops	P Many
3	5 loops	P Few
4	7 loops	P Few
5	9 loops	P Many
6	0.1 c.c.	P Many
7	0.2 c.c.	P Many
8	0.3 c.c.	P Many
9	0.4 c.c.	P Many
10	0.5 c.c.	P Many

CULTURES FROM DUODENUM BELOW  
FISTULA

Tube No.	Amount of Intestinal Contents Used.	Result.* Colonies.
1	3 loops	N
2	5 loops	N
3	7 loops	P 1
4	9 loops	N
5	12 loops	N
6	.25 c.c.	P 4
		2
7	.5 c.c.	N
8	.75 c.c.	N
9	1 c.c.	P 4
		5
10	2 c.c.	P 3
		6

CULTURES FROM UPPER ILEUM

Tube No.	Amount of Intestinal Contents Used.	Result Colonies.
1	3 loops	N
2	5 loops	N
3	7 loops	N
4	9 loops	N
5	12 loops	N
6	.25 c.c.	N
7	.5 c.c.	P 2
		5
8	.75 c.c.	N
9	1 c.c.	P 11
		3
10	2 c.c.	N Overgrown

CULTURES FROM LOWER ILEUM

Tube No.	Amount of Intestinal Contents Used.	Result Colonies.
1	3 loops	N
2	5 loops	N
3	7 loops	N
4	9 loops	N
5	12 loops	P 2
6	0.25 c.c.	N
7	0.5 c.c.	P 4
		4
8	0.75 c.c.	N Overgrown
9	1 c.c.	N Overgrown
10	2 c.c.	P 3
		6
		Overgrown

CULTURES FROM CECUM

1	1 loop	N
2	2 loops	N
3	3 loops	N
4	4 loops	N
5	5 loops	N

CULTURES FROM LARGE INTESTINE

1	1 loop	N
2	2 loops	N
3	3 loops	N
4	4 loops	N
5	5 loops	N

CULTURES FROM GALL-BLADDER

Tube No.	Amount of Bile Used.	Result Colonies.
		2
1	3 loops	P 4
2	6 loops	P 5
		3
3	0.3 c.c.	P 19
		43

CULTURES FROM URINE IN BLADDER

Tube No.	Amount of Urine Used.	Result Colonies.
1	3 loops	N
2	6 loops	N
3	0.5 c.c.	P 3
		1

For this entire experiment fifty-six bouillon tubes were inoculated and from these 112 agar plates were made twenty-four hours later. Two plates were made from each tube.

\* P = *Bacillus prodigiosus*. N = Negative.

## BACILLUS PRODIGIOSUS INOCULATED INTRAVENOUSLY INTO RABBIT AFTER DOUBLE LIGATION AND DIVISION OF DUODENUM AND LIGATION OF PANCREATIC DUCT

*Experiment 26.*—Previous to inoculation the duodenum was doubly ligated and divided just below the entrance of the bile-duct. The pancreatic duct was also ligated. One loop of culture inoculated as soon as animal recovered from operation; one hour later animal chloroformed to death. Positive Cultures: None. Negative Cultures: Duodenum 10, ileum 5. Remarks: One, three and six loopfuls of intestinal contents were transferred to broth in this experiment and the two following.

*Experiment 27.*—One loop of culture material injected; rabbit chloroformed one hour after inoculation. Positive Cultures: Duodenum above ligature 2, lower duodenum 2, ileum 1. Negative Cultures: Duodenum above ligature 1, lower duodenum 3, ileum 4.

*Experiment 28.*—Repetition of Experiment 27. Positive Cultures: Duodenum above ligature 3, lower duodenum 3. Negative Cultures: Duodenum above ligature 2, lower duodenum 9, ileum 5.

## BACILLUS PRODIGIOSUS INJECTED INTO JUGULAR VEIN OF DOG.

*Experiment 29.*—Intestinal fistula made below entrance of bile duct and pancreatic ducts. Animal fed through fistula for forty-eight hours, and starved twelve hours preceding inoculation. Ends of fistula closed off. Four loops of culture in 4 c.c. of salt solution injected. Dog chloroformed two hours later.

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## EXPERIMENTAL LUNG ANTHRACOSIS

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Recent work, especially in France and Germany, has again opened the question of the origin of lung anthracosis. Calmette and others of his school at Lille have observed it in animals fed with charcoal, but failed to find a true parenchymatous anthracosis when the substance was merely inhaled, the stomach absorption being excluded by cutting and tying the esophagus. They therefore concluded that lung anthracosis is usually of intestinal origin, and believe that the continual passage of particles through the lymphatic system to the right heart in time breaks down the resistance of this natural barrier to the progress of foreign bodies from the intestine to the general circulation. Drawing attention to the analogy between lung anthracosis and lung tuberculosis, they point out that the latter may be of intestinal origin as well as the former. This analogy tremendously increases the importance of the work, and has led many others to repeat or modify Calmette's experiments.<sup>5 6</sup> Most investigators have been unable to verify his results, although a few seem to have succeeded in doing so.

Charcoal, carmin, cinnabar and osmic acid have been used. They have been introduced into the stomach by mouth, by a catheter and by laparotomy; into the peritoneal cavity by injection, and into the intestine by laparotomy. After the lapse of a certain time the animal is killed and the lungs examined either macroscopically or microscopically.

None of this work, however, has been entirely free from error of experiment or observation.

When the substance is swallowed, some may be inhaled; when introduced by the catheter, the catheter may be improperly passed into the trachea; when the esophagus is cut and tied or a laparotomy performed, the anesthetic may cause plugging of the bronchi by mucus, and general shock and lessened vitality further complicate the experiment. Inhalation experiments without tying the esophagus are useless, as some of the substance is certain to be swallowed.

The best method seems to be to inject the foreign substance into the peritoneal cavity, there being little shock and no anesthesia required. It is true that it is not directly introduced into the intestine, but Miro-



nesco.<sup>11</sup> Macieszka,<sup>12</sup> Tsunoda<sup>13</sup> and others have established the fact that the intestinal wall is permeable to non-motile particles.

The choice of the substance to be injected presents new difficulties. Lamp-black or some other form of carbon has been most generally used. It is stable, non-poisonous, not affected by the body fluids and easily recognized. A large proportion of adult animals, however, show a natural lung anthracosis, and it is impossible to differentiate between a black substance preexisting in the lungs and that introduced as a result of experiment. The alternative of young (not full-grown) animals suggests itself, but Calmette found that these always give negative results, perhaps because the mesenteric glands have not yet become permeable to foreign particles.

Carmin is much less stable than lamp-black. Little is known about the action of the body fluids on this substance, and even if it can be definitely proved to be absent from the lung tissue, this may be due to decomposition or absorption before it has had time to reach that organ.

No red or yellow pigment can be recognized easily by macroscopic examination when present in small quantities in an organ so vascular and so subject to changes of gross appearance as the lung. Microscopic examination may be deceptive owing to variations of light and refraction. The same objections hold good for cinnabar, which has the added disadvantage of toxicity.

In a previous paper I described some attempts I had made to overcome these objections by the use of ultramarine blue, one of the most stable of the blue, green or violet pigments, which seemed to be ideal for this purpose. Negative results were obtained, but these can not be accepted as final, for here again little is known of the effect on ultramarine blue of prolonged contact with the body fluids.

In this preliminary paper I outlined a method which seems to eliminate the errors of experiment and observation just mentioned. Talc is the foreign substance used. It is non-poisonous, extremely stable, and can be recovered unchanged, and thus positively identified. There is no personal equation, no error of observation. The talc remains as talc and can be freely examined by a number of persons and kept indefinitely.

Purified talc is injected into the peritoneal cavity and after a certain time the animal is killed and the organ under observation completely burned in a platinum crucible. The residue is treated on the water-bath with hydrochloric acid. In control experiments in which only a few milligrams of talc were added to the viscera, this substance was easily recovered and recognized.

EXPERIMENT 1.—Guinea-pig; weight 555 gm. Two gm. of purified tale, suspended in 5 c.c. sterile distilled water, were injected into the peritoneal cavity. Forty-five hours later the guinea-pig was killed with chloroform.

*Autopsy.*—There was some free tale in the abdominal cavity, the mesenteric lymph vessels and mesenteric glands contain tale. No tale could be recognized macroscopically in the thoracic cavity. The lungs were washed and completely burned in a platinum crucible, and the residue treated with hydrochloric acid on the water-bath. The residue was completely dissolved and the resulting solution was clear, containing no tale. The liver was carefully washed, burned in a platinum crucible and treated with hydrochloric acid, as before described. The solution was clear. The spleen was washed and treated in the same manner. No tale was found.

EXPERIMENT 2.—Guinea-pig; weight 420 gm. Two gm. of purified tale in 5 c.c. distilled water were injected into the peritoneal cavity. Fifty-two hours later the guinea-pig was killed with chloroform.

*Autopsy.*—No free tale was found in the abdominal cavity. The mesenteric lymph-vessels and mesenteric lymph-glands contained tale. No tale could be seen on macroscopic examination of the thoracic viscera. The lungs were washed, burned and treated as before. The residue dissolved completely, containing no tale. The liver, spleen and kidneys were treated in the same manner, with the same result.

EXPERIMENT 3.—Control. A piece of sheep's liver to which a few milligrams of tale had been added was completely burned in a platinum crucible, and the residue treated on the water-bath with hydrochloric acid. The tale was recovered unchanged and recognized.

EXPERIMENT 4.—Guinea-pig; weight 640 gm. Two gm. of tale and one-half gram of charcoal, suspended in 5 c.c. distilled water, were injected into the peritoneal cavity. The charcoal was added to make easier the macroscopic observation of the distribution of the tale. Forty-nine hours later the animal was killed with chloroform.

*Autopsy.*—Much free tale and charcoal were observed in the peritoneal cavity. The mesenteric lymph-vessels and glands contained tale and charcoal. The surface of the liver and spleen were covered with a black deposit. No sign of charcoal was observed in the thorax. The lungs were removed, washed and completely burned, and treated as before described. No tale was found. The liver and spleen were each carefully washed free from surface deposits and burned in the same manner, with the same result.

EXPERIMENT 5.—Guinea-pig; weight 820 gm. Four grams of tale and 1 gm. of charcoal, suspended in distilled water, were injected into the peritoneal cavity. Twenty-six days later the animal was killed.

*Autopsy.*—A slight deposit of carbon was observed at the site of injection. No free foreign matter was found in the peritoneal cavity; a few of the mesenteric glands contained a black deposit. No black deposit or tale was observed in the thoracic cavity. Lungs, liver and spleen were removed and treated as before. The result in each instance was a clear solution containing no tale.

These experiments show that tale is not carried from the peritoneal cavity and mesenteric lymph-nodes to the lungs during the maximum period of observation of these animals. They do not prove that charcoal is not thus carried, but they add largely to the probability that it is not.

While it may be asserted that results obtained with talc cannot be applied to charcoal, on account of the great difference in density, size of particles, etc., it should be remembered that the silicates, under certain circumstances, form the basis of lung deposits, a natural lung silicosis being sometimes observed in potters and quarry workers. Although the analogy between lung silicosis and lung anthracosis is certainly as great as the analogy between lung anthracosis and lung tuberculosis, it cannot be held that these results apply conclusively to ingested tubercle bacilli. They do, however, add important evidence against the theory that the origin of lung deposits is by way of the mesenteric lymph-channels.

I have in view the continuation of this work over a longer period of time, using impalpable silicic acid and the same method of identification.

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## THE INDUCTION OF PANCREATIC ACTIVITY BY THE REMOVAL OF THE ADRENALS\*

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We reported before the Association of American Physicians in Washington, May, 1909,<sup>1</sup> the results of our work on the relation of certain ductless glands to the pancreas, and we there offered among other conclusions, the following:

1. The inhibition of pancreatic secretion by adrenalin is independent of systemic blood-pressure, as shown by its persistence when the blood-pressure is much below normal and by other evidence.
2. The inhibition by extracts of pituitary and suprarenal bodies also occurs when the pancreas is stimulated by its normal excitant, hydrochloric acid in the duodenum.
3. The evidence now at hand indicates that the suprarenal glands exercise an inhibitory power on the pancreas, and that on the removal of this influence by ablation the pancreas secretes more actively.
4. The agonal period of life (in the sense described) is generally accompanied by an exacerbation of the normal rate of pancreatic flow.

Our report was preliminary, and although our conclusions were strongly suggested by the evidence at our command, they were not supported by that number and variety of experiments which alone could offer substantial proof.

In order to ascertain the truth, and definitely to corroborate or disprove our conclusions, we have devoted the past year to a repetition and amplification of our earlier work, together with certain changes in its terms, on such a scale as would place the results to be obtained by these methods beyond reasonable doubt. The results so obtained we wish now to report.

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\* Reported before the College of Physicians, Philadelphia, June 1, 1910.

<sup>1</sup> From the S. Weir Mitchell Laboratory of Physiology and the Woodward Fellowship, Pepper Laboratory of Clinical Medicine, University of Pennsylvania.

1. Pemberton, R. and Sweet, J. E.: Further Studies on the Influence of the Ductless Glands on the Pancreas, *Tr. Assn. Am. Phys.*, 1909, xxiv, 502.

## PRIOR WORK

For three years past we have been concerned with the question of pancreatic activity in several of its phases, and have shown that extracts of the adrenal and pituitary glands, when injected into the system, cause a diminution or cessation of the flow of juice from the pancreas, whether this flow be caused by the normal chyme, hydrochloric acid artificially placed in the duodenum, or duodenal secretin intravenously injected. We have obtained this result from no other tissues as yet, though many have been tested; but certain extraneous agents, among them nicotine, are reported to have an analogous action.

The *modus operandi* of this phenomenon is still *sub judice*, though it has been attributed to vasoconstriction. Some evidence supports this, not conclusively as yet, but the observations here to be presented seem to throw further light on the matter.

Other relations between the pancreas and the ductless glands of the body we have elsewhere taken up and need not now consider; but the connection just mentioned between the pancreas, on the one hand, and the adrenals and the pituitary, on the other, concerns us especially.

## PRESENT PROBLEM

If the intravenous injections of extracts of the suprarenal and pituitary bodies cause inhibition of the pancreatic flow, after whatever method of excitement, the question is at once presented as to what would be the effect of removing from the pancreas such influence as these glands normally presumably exert. Evidence on this latter point would not only be of interest in enlarging our present conceptions of interglandular action, but would also tend to act as a check on the former observation and possibly help elucidate the mode of action.

As we have elsewhere pointed out, the difficulties to be met in such a problem are very great, and necessitate the utmost care in the interpretation of results as well as in obtaining them. The terms of a biologic experiment are rarely exact, and in this particular instance we have to deal with many factors that are indefinite and poorly understood. In addition to this, the time required for a single experiment in some instances has been so great as to preclude its frequent repetition, such experiments requiring the practically undivided attention of two observers over periods of seventeen or eighteen consecutive hours.

## METHOD OF WORK

Our method was as follows: We established in fasting dogs a temporary pancreatic fistula by introducing into the pancreatic duct a can-

nula through which the flow of juice could be observed and measured. This flow was recorded by interruptions of the base line on a kymograph-ion tracing as the juice passed divisions on the cannula. The records are preserved in the form of continuous tracings of each experiment, from the beginning of anesthesia until death.

Coincident tracings were made of the respiratory movements, blood-pressure, and the time in seconds. The details of our work hardly call for explanation here, as they are fully set forth in our previous contributions on this topic.<sup>2</sup>

Our animals were under complete surgical anesthesia by ether from the beginning of the experiment until the end.

Following the establishment of the above procedures, the adrenals were removed through a large median incision, which also served for the pancreatic manipulations. The adrenals were removed by blunt dissection, the right usually first, since it is the less accessible and operation on it produces a greater disturbance to the general economy than it does in the case of the left gland.

Sometimes the order of procedure varied from that just given, though we usually found the latter the most expedient. Animals which have been subjected to bilateral ablation of the adrenals withstand poorly any further trauma, even that of establishing a connection with the respiratory tambour or blood-pressure manometer, and not infrequently succumb prematurely.

The total number of our experiments was forty-one, exclusive of a number devoted to certain incidental features which will be mentioned later. This does not include those observations on which we made our first tentative report.

Our object was to observe the normal rate of pancreatic secretion under the conditions of a temporary fistula, and then to observe the rate after the removal of the adrenals. In our work of a year ago we had not realized sufficiently the importance of using only fasting dogs, and, as a consequence, the question became complicated by the presence of a flow from the pancreas from digestive causes. We know now that the phenomena to be considered are not essentially altered under these circum-

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2. Sweet, J. E. and Pemberton, R.: Experimental Observations on Secretin With Special Reference to Diabetes and Malnutrition, *THE ARCHIVES INT. MED.*, 1908, i, 231; The Inhibition of Pancreatic Activity by Extracts of the Suprarenal and Pituitary Bodies, *ibid.*, 1908, i, 628; 1908, ii, 295; Further Studies on the Influence of the Ductless Glands on the Pancreas, *ibid.*, 1910, v, 466.

stances, and are indeed rendered very graphic and striking; but the interpretation of results is made much more difficult by this complication.

In the experiments now discussed the dogs were, therefore, animals which had been fasted for thirty-six hours, and, except for one or two which had broken loose and had foraged, unknown to us until later, the gastro-intestinal tract was free from food. The experimental and control animals were selected to conform in size as nearly as possible, and were often of the same breed.

#### FINDINGS IN NORMAL DOGS

In normal dogs under ether there is a slight tenesmus, even during a fast, for the pancreas to secrete. This may be incompressible for hours at a time or even apparently absent, but, sooner or later, it generally shows itself, so that toward the end of a period of observation there is usually a well-marked, though relatively slight, flow. This may, however, be more pronounced throughout, and some dogs, for reasons which we do not understand, may secrete with fair activity. Each dog forms more or less of a law unto itself and, if the flow is sluggish at the start, it never becomes rapid or prolonged later. Within the terminal or agonal moments it often undergoes a distinct exacerbation. The total amount of flow in normal animals may therefore vary between a practically unmeasurable quantity and seven to nine cannulafuls in the course of ten to seventeen hours.

If, as often occurs on introducing a cannula into an organ so vascular as the pancreas, there be a slight hemorrhage and the clear juice become clouded by blood, doubt at once arises as to whether the duct is clear; and, if the flow be sluggish, the condition simulates obstruction so perfectly that only the course of events, or autopsy, after perhaps sixteen or eighteen hours, will show the truth. We know no way of obviating this, as the cannula cannot be removed frequently from such delicate structures. If, however, the duct be clear, the meniscus of juice in the tube moves with the movements of respiration and affords a fairly reliable index of patulency. The evidences of flow when the duct is first opened are also of value as indicating what may probably be expected from the gland. Also, if there be obstruction, and secretion be free, the gland may appear somewhat edematous.

In normal dogs the blood-pressure is but little affected by the operative proceedings described, and it falls only after prolonged etherization or as the strength of the animal fails. This may be after a variable period which sometimes much exceeds seventeen hours, the only condition

to determine death being, apparently, the relation of the amount of ether to the animal. In other words, if the ether is carefully watched, the dog will live for a long period; but, if the ether is carefully pushed, the end can be materially hastened.

In those subjects which have survived so long we have finally given more ether until the blood-pressure slowly fell, since otherwise the observations would have been essentially on normal dogs under conditions which would not serve as controls for the phenomena we wished to examine.

#### FINDINGS AFTER REMOVAL OF THE ADRENALS

On the other hand, in contrast to the results with normal animals, if the adrenals be removed, the picture becomes very different. The operation of ablation itself produces considerable shock, and when after some oscillation the blood-pressure becomes steady, it is generally found to be significantly lower. This does not seem to be due to the operative disturbance alone.

The right adrenal, as remarked, is difficult to remove, but the left can be taken out with relative ease in a few minutes. Now, if the right alone be removed, the shock of ablation *per se* is very marked, but is not greatly increased if the left be also removed, and animals so treated have lived almost as long as the normal under ether; that is, ten to fifteen hours. When both adrenals are removed the pressure never returns to a height approximating its former level, but suggests the condition seen after many hours in the normal animals. It declines more or less rapidly until the animal dies after a variable period, say six to eight hours. During this period, in every instance encountered so far, the pancreas begins shortly to secrete, and increases in the rapidity of output until in some cases this secretion is so great as to make a record of it difficult, except in terms of five divisions of the cannula as units. The number of cannulas filled is consequently vastly in excess of those seen with normal dogs, and indicates a proportionately greater formation of pancreatic juice.

There is no definite time of the experiment or condition of blood-pressure at which the flow begins, as the factors which regulate the flow seem to depend, for the most part, on the idiosyncrasies of the dog; but, in general, it can be said that it begins in not less than two hours nor more than five.

It can be seen, therefore, that no dependable statistical average can be made of the rate or quantity of flow, or of the other contributory factors under which it takes place; but this much seems definitely sure that,



after removal of the adrenals, there always occurs a flow, and that this flow may reach such proportions that we are unable to duplicate it, save by the injection of powerfully active duodenal secretin.

Indeed, if the animal has not fasted, ablation of the suprarenals induces such activity that even the results sometimes obtained from the last-mentioned stimulus may be exceeded. The contrast between normal control animals and those without their adrenals is, therefore, very marked.

It is important to note that this flow begins earlier, that it lasts very much longer, and that it is greater in volume or rate, or both, than the normal output, despite the fact that death occurs much sooner. Once established, however, the duration of the flow is limited, apparently, only by the life of the animal. The longer the animal lives, the longer secretion takes place.

These facts must be borne in mind in comparing, for example, a dog with adrenals ablated, whose pancreatic flow is sluggish at the start, with a normal dog whose pancreatic flow is active at the start; and especially is this true if the normal dog lives long and secretes a number of cannulafuls during, perhaps, sixteen hours, while the ablated dog shows an early exacerbation, perhaps, but also early death, before the total output is very great.

While there is nearly always some little flow from the normal animal, however, it rarely passes a point which we have grown to regard as the usual limit under such circumstances, namely, about six to eight cannulafuls in a period of possibly as much as seventeen hours.

More frequently, however, there is almost no flow at all, save at the end, when there supervenes a condition which simulates in some respects that induced earlier by the removal of the adrenals. There seems to be an analogy between these two conditions; and the normal dog may conceivably reach a state in which his system as a whole presents apparently the same need of suprarenal activity as does the animal with adrenals ablated. Whether this is the case, however, is, as yet, purely conjectural.

There is here, however, one point of interest, which seems to us to throw light on the *modus operandi* of the feature under discussion. As has been said, the inhibitory action of epinephrin\* has been ascribed<sup>3</sup> to its vasoconstrictive power. This may be justifiable, though, as we have elsewhere stated, some evidence opposes it. If the flow from the pancreas

\* Adrenalin is the variety of epinephrin used throughout these experiments, except in some early work where the change was noted.

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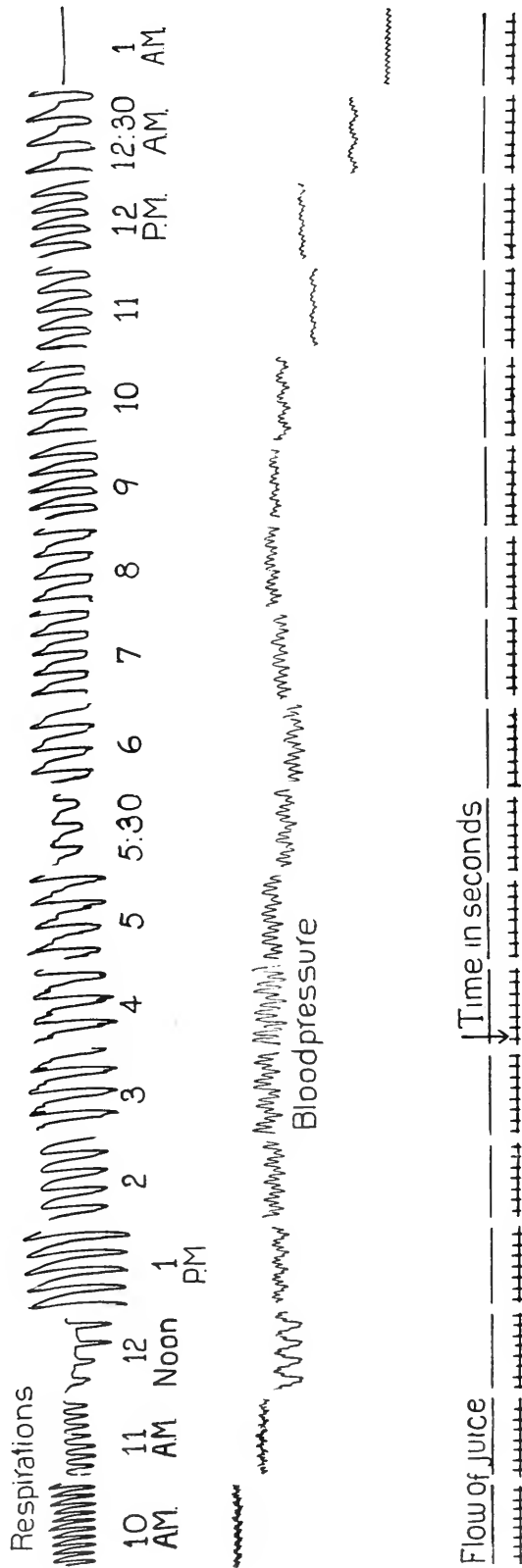


Fig. 1.—Tracing made Feb. 8, 1910, from normal control, with adrenals intact, showing fall of blood-pressure in a lengthy experiment without flow. Ether begun at 9:53.



Fig. 2. Tracing made Dec. 15, 1909, from dog with adrenals removed; right adrenal removed 11:58 a. m., left adrenal removed 12:02 p. m.



Cannula emptied to  
division 15



Fig. 3.—Tracing from same experiment as Figure 2, showing rate



Cannula

nnula emptied to division 22

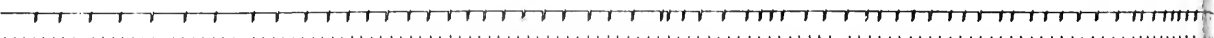
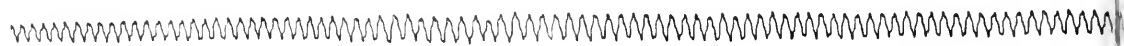


Fig. 4.—Tracing from same experiment as Figures



Cannula emptied

22

31

35

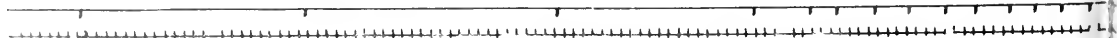
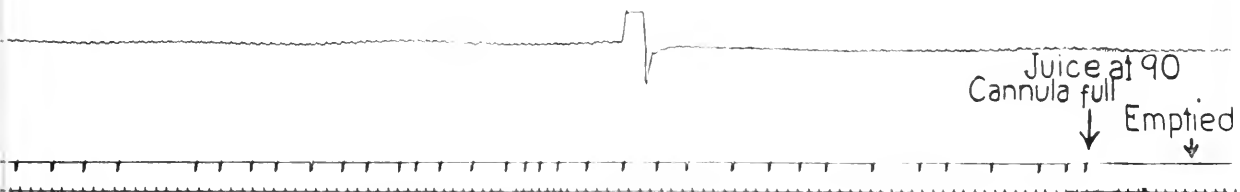
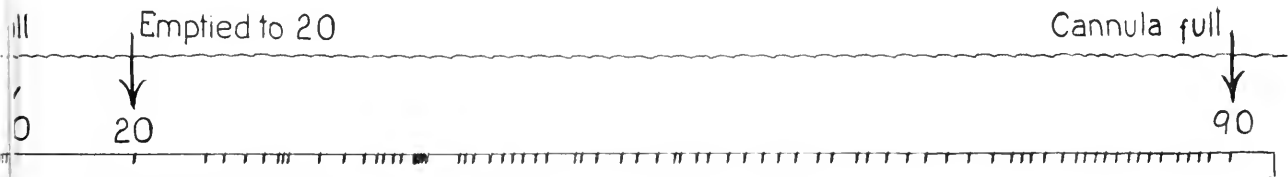
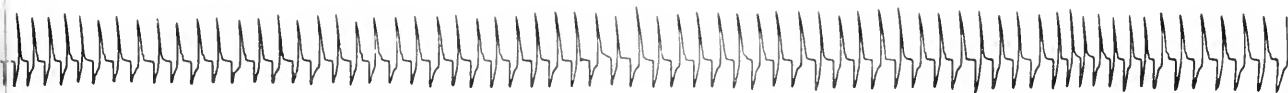


Fig. 6.—Tracings from same experiment as Figure 5, showing



Juice at 90  
Cannula full  
↓  
Emptied  
↓

of flow at 5:48 p. m., and covering the filling of one cannula.



2 and 3, showing rate of flow at 7:04 p. m.



Cannula full  
↓  
90

flow of juice with a fairly high blood-pressure at 1:38 p. m.

be inhibited by vasoconstriction and a high blood-pressure, it would seem that the opposite condition of affairs would be conducive to a flow. We know that a low blood-pressure alone will not lead to this. If, however, on removing the adrenals we find a marked tendency to secretion, at the same time that the blood-pressure is low or falling, we naturally incline to associate the events, and to regard one as perhaps causative of the other. We have here, however, evidence that this is not the case, because, if a normal dog be watched, as described, the blood-pressure will be found to fall just as low as it does with the dogs whose adrenals have been ablated and remain low just as long, or perhaps longer, but no flow occurs, or at most one which is manifestly inferior.

The problem is not settled by this observation, but the latter strongly suggests that the relation of the adrenals to the pancreas is very close. Taken in connection with the inhibition of pancreatic flow by the intravenous injection of epinephrin, the induction of a flow by the absence or insufficiency of the adrenals presents a potent argument for specificity of control by one gland over the other. This control seems none the less specific, even though possibly caused by the vasomotor properties of epinephrin, but, in the observation just recorded, there is apparently evidence that vasomotor control is not the only factor operating. Even if it is the only factor, the pancreas shows such a degree of susceptibility to the presence or absence of epinephrin as to indicate specificity on this score.

We have tried to establish controls, and have attempted to produce the same results by means of some abdominal injury, on the basis that nervous stimulation or inhibition produced by the removal of the adrenals, induces secretion. Such action would presumably take place much sooner than does the flow in question, but, to investigate the matter we have, in ten instances, removed one adrenal only, especially the right, in order to produce approximately the same amount of disturbance and trauma that occur when both adrenals are removed. This latter injury would be closely simulated, since the removal of the left adrenal, as elsewhere remarked, is relatively easily and quickly accomplished. The left adrenal has also been removed alone, and, again, we have handled and bluntly dissected both adrenals, about as we do in extracting them, without, however, destroying their functioning power, or blood-supply. In all these cases, however, we have been unable to produce the conditions described as occurring when both adrenals are removed. The instances of removal of one adrenal were about equally divided between a moderate flow and no flow at all, and the instance of blunt dissection of both

adrenals without conscious injury to their function, gave absolutely no flow whatever.

It will be noted in the accompanying protocols that in some instances of ablation the dog died before evidence could be obtained one way or the other. Again, others died when a flow had but just begun. These latter distinctly illustrate the point at issue, and yet the accidents and uncertainties of anesthetization make statistical use of them practically impossible.

In a few words, the order of events seems to be that a dog with the adrenals removed gives a marked flow; a dog with one adrenal removed tends to give some flow, though less and often none; and a dog with the adrenals intact gives practically no flow at all, or relatively little.

We have also introduced a cannula into the hepatic duct to determine if the output of bile were increased, but have observed no flow in the instances tried, although the pancreas secreted actively. We expect to try the same thing on the salivary and other glands.

#### ALLIED PROBLEMS

We feel that, with the methods of procedure hitherto used, the subject is not susceptible of much greater solution, and, because of our desire to approach it by other means, it seems wise to publish what we have done to date before taking up other measures or topics. Some of the studies which we have in mind are:

1. Experiments with duodenal secretin and epinephrin on dogs with adrenals ablated when showing a flow or a beginning tendency to flow.
2. Examination of the pancreatic juice secreted at various periods in all the conditions described above.
3. Transfusion of the blood from a normal dog into one whose pancreas is secreting after ablation.
4. Transfusion of the blood of a secreting dog with adrenals ablated into a normal dog whose pancreas can be watched after the usual method.
5. The production of hemorrhage in a secreting dog with adrenals ablated.
6. Efforts to detect epinephrin in the blood at various periods of the above experiments.
7. Destruction of the adrenals by agents which will not seriously disturb the general economy.
8. Removal of the pituitary body under analogous circumstances, etc.

A number of such problems demands investigation and promises much information of value in regard to our present imperfect conceptions of the adrenals and other ductless glands.

#### OBSERVATIONS ON DUODENAL SECRETIN

One series of observations, in line with the projected work just outlined, and planned with the idea of throwing light on the main problem, we have taken up. It is not as yet complete, because the methods employed have proved inadequate to a satisfactory definition of the results, but there seems to be indicated a condition which is at once surprising and indicative of interesting possibilities.

On observing the marked flow of pancreatic juice in dogs whose adrenals had been removed, it seemed to us that the pancreas might be conceivably acting as the result of a change in some one of the stimulating factors rather than as a result of the removal of inhibition alone. Or, again, a combination of these might be operative. We therefore turned our attention to the secretin content of the duodenum with a view to ascertaining whether or not it was affected by the absence of the adrenals or their products.

#### METHOD OF WORK

An examination of this kind proved troublesome because of the difficulty in having the varying terms of the experiment constant. It was necessary to make a preparation of secretin from the intestines of a dog with adrenals ablated, and to compare it with secretin made from a normal dog killed for that purpose. It was then necessary to compare secretin made from a normal dog which had died under similar conditions of anesthesia after a long period, with secretin from a normal dog killed for the purpose.

These comparisons were made by injecting the solutions into a normal dog, the activity of whose pancreas could be observed by means of a cannula in the pancreatic duct. Coincident records were made of the blood-pressure and respiratory movements of the injected dog, as well as the time in seconds. It was desirable to compare directly secretin made from a dog with adrenals ablated, with that from a normal dog which had died after a comparatively long etherization, the flow from whose pancreas had been observed and found to be slight. Because of the physical limitations to our facilities for work, however, this last could not



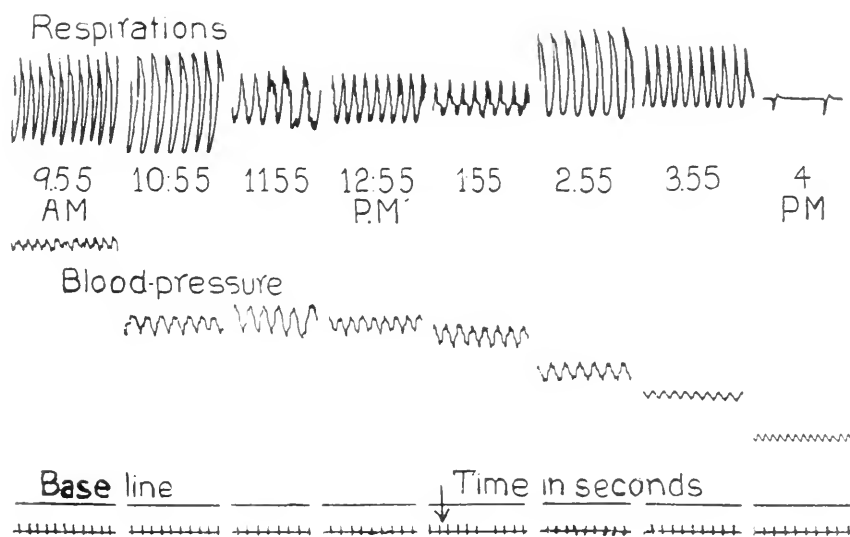


Fig. 5.-Tracing made Feb. 17, 1910, from experiment on animal with adrenals removed, showing flow of juice, with a high blood-pressure. Right adrenal removed 10 a. m., left adrenal at 10:32 a. m. In this tracing, inadvertently, no record was taken of the flow at the period shown in the segment. The flow appears on the next two tracings.

be accomplished, and we had to compare each of these with a control. Such controls varied among themselves according to the varying amounts of secretin in the intestines of the normal dog, but were, of course, constant for given comparisons.

The secretin solutions were made by taking definite lengths, two to four feet, of intestine from the experimental and control animals and removing the mucosa. Equal weights of these scrapings were then ground up with sand for equal periods in acid of the same strength and treated as described elsewhere, making two solutions, one control and one experimental.

These solutions were decanted and strained. In some of the earlier experiments, when the intestine first worked up gave heavier and more wise normal dogs whose pancreatic activity or inactivity had been like in making the dilutions of the second; but such cases were about equally divided between the control and the other instances, and were later avoided entirely.

Where delay was inevitable between death and the preparation of secretin from an animal which had been operated on, the control dog was killed at the time the former died, and the intestines from both were kept on ice for the same period. In the final tests of these preparations equal amounts were of course used, from 3 c.c. to 10 c.c., generally about 5 c.c., and alternately injected into the femoral vein after the first and usually more active response had subsided.

#### FINDINGS

For convenience of reference we shall designate the secretin made from dogs whose adrenals had been ablated after many hours of observation and flow, as "terminal adrenal secretin" or T. A. S.; that from otherwise normal dogs whose pancreatic activity or inactivity had been likewise observed over many hours until death, as "terminal normal secretin" or T. N. S.; and that from dogs killed for normal control secretin, as "normal secretin" or N. S. All these dogs had fasted for thirty-six hours.

In six experiments in which secretin from a dog whose adrenals had been ablated was tested against normal control secretin, it was weaker twice; twice of about equal strength though possibly stronger; and twice, stronger than the control.

In five experiments in which secretin from an intact animal which had been observed over many hours of relative pancreatic inactivity was tested against a normal control secretin, it was in every instance distinctly weaker.

That the terminal normal secretin should be weaker than the normal secretin was perhaps to be expected *a priori*.

On the other hand, that terminal adrenal secretin, T. A. S., should ever be as strong as the control from a healthy fresh animal, N. S., is surprising, especially in view of the consistently uniform inferiority of the terminal normal secretin (T. N. S.) as compared with the normal secretin (N. S.).

In point of fact, however, the terminal adrenal secretin, T. A. S., was sometimes actually stronger than the secretin from a strong healthy dog. It can hardly be doubted that it would have shown a proportionately greater contrast of strength, if tested against its true analogue, terminal normal secretin (T. N. S.).

The table shows this more graphically:

N.S.	>	T.N.S.			
N.S.	>	T.N.S.			
N.S.	>	T.N.S.			
N.S.	>	T.N.S.			
N.S.	>	T.N.S.			
N.S.	<	T.A.S.	See exp. 44	1	12 10
N.S.	<	T.A.S.	See exp. 42	1	7 10
N.S.	>	T.A.S.	See exp. 47	2	18 10
N.S.	>	T.A.S.	See exp. 43	2	9 10
N.S.	=	T.A.S.*	See exp. 45	2	13 10
N.S.	=	T.A.S.*	See exp. 46	2	14 10

\* No definite preponderance in favor of either.

#### DISCUSSION OF FINDINGS

We must infer from this that our experiments, as far as they go, indicate some peculiarity of the duodenal mucosa in dogs which have had their adrenals removed. By virtue of this it seems to have properties

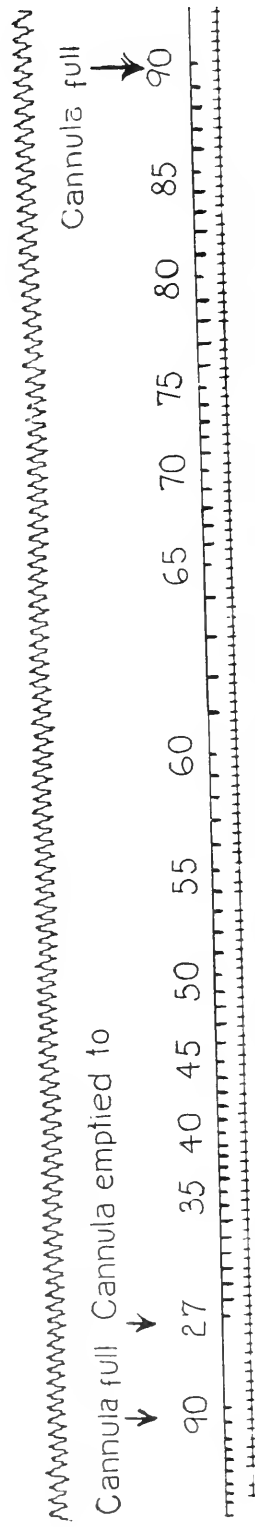


Fig. 7. Tracing from same experiment as Figures 5 and 6, showing flow of juice, with a fairly high pressure at 2:05 p. m.

more stimulating to the pancreas, when extracts are made from it, than has the mucosa of normal dogs subjected to the same procedure, or even, sometimes, that of healthy vigorous animals freshly killed.

If these results be corroborated, they may prove to be of further interest. Not only would they further indicate a control over the pancreas by the adrenals, but they would suggest a view of the adrenals as organs related to intestinal digestion. This is by no means proved as yet, and we do not wish to be interpreted as postulating it, but the evidence along this line is not without interest.

It is interesting to note that, if the pancreas secretes more actively in the absence of the usual suprarenal products, vaso-motor or of whatever nature, this activity is apparently supplemented and strengthened by the presence in increased amounts of the normal excitors in the intestine. These may be manifestations of one and the same process, hyper-stimulation from the intestine, but we are not inclined to this view, as in some instances in which we recorded a very active flow, the activity of the terminal adrenal secretin was not proportionately great, though apparently always greater than the terminal normal secretin. It is conceivable that the terminal adrenal secretin is stronger than the terminal normal secretin, because the terminal adrenal dogs die before it becomes so much reduced as in the others, and yet many of them live so long as to make this difference negligible. This would not explain, in any event, those cases in which the terminal adrenal secretin was equal to, or in two cases stronger than, the normal.

As to the cause of the presence of more than the normal amount of secretin in terminal adrenal dogs, no answer can be given except that, if vascular control be the explanation of this property of the suprarenals, a conceivable determination of more blood to the intestinal mucosa in the ablated animal might afford more of the factors from which the excitor is normally formed. If this be the case, however, it merely affords that concrete explanation of action, which must ultimately exist in any event.

Observations of this general type on the factors which conduce to the formation of secretin may throw light on its nature and the substances that are necessary to its composition.

One or two further points require notice. The first is that, noticing frequently in cases of terminal adrenal flow a congestion of the viscera, we thought it possible that stasis might be the cause of the pancreatic

output, although observations in the past by others<sup>4</sup> have shown that there occurs no post-mortem flow from the pancreas, due to stasis.

As reference to our protocols will indicate, we studied every animal at autopsy with a view to observing this and other features, but could find no evident relation between the extent and degree of congestion and the flow from the pancreas. In no instance did the pancreas at autopsy show any marked degree of congestion. It never showed the picture of passive congestion such as is caused by interference with the portal outflow, but was often pale.

Occasionally there occurs, after removal of an adrenal gland, a slow oozing from its previous site which is not apparent at first, and is hard to foresee or control. This happened in four instances. In one of these, we had looked for the usual terminal adrenal flow and were surprised at not getting it until the somewhat early fall of blood-pressure and premature death of the dog revealed considerable hemorrhage into the abdominal cavity.

Such observations have inclined us to believe that under circumstances in which a terminal adrenal flow is to be expected, hemorrhage will prevent it, and, indeed, it is possible that it will also prevent the greater activity of secretin made from terminal adrenal mucosa. This may explain the only two instances in which terminal adrenal secretin was weaker than normal secretin as indicated in the table (Experiments of Nov. 7, 1910, and Nov. 8, 1910). There also seems to be in this an argument against the probability that a low blood-pressure *per se* is the determining factor in the flow under discussion, since hemorrhage must contribute to conditions of low blood-pressure but, at the same time, apparently prevents or modifies the flow.

We wish here to call attention again to a certain feature which we emphasized in our first contributions on pancreatic activity.<sup>2</sup>

Among other conclusions there presented were the following:

1. There would seem to be some factor which makes the preparation of secretin from human intestines more difficult than from the intestines of some animals.
2. This factor may depend on the relatively great abundance of membrane in these animals and consequently greater amount of prosecretin.
3. The abundance of mucosa may be in part a provision of Nature in order that the strongly acid chyme of some animals may meet with a quantity of pancreatic juice sufficient to neutralize it and effect digestion.
5. Dieting and fasting seem to have no appreciable effect on the activity of an extract.
6. Time elapsed between death and the preparation of the extract (within limits) does not seem to be a factor. . . .

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4. Bainbridge: Brit. Jour. Physiol., 1906, xxxiv, 275.

It will be noticed that prosecretin is apparently abundant in the duodenum of dogs and that it is more difficult of detection in the duodenum of human beings. In these latter instances, however, the quantity of mucosa obtained is frequently abundant, and gives no *a priori* indication of the difficulty to be met in obtaining an active extract of its prosecretin. Granting that the mucosa is less plentiful in human beings, it would be expected that secretin solutions made therefrom would be inferior to those made from dogs, but there still remains the difficulty of accounting for the apparent entire absence of secretin in the cases of various diseases which we reported.

It appears that our recent observations help to elucidate this point. We have seen that, in every case examined, the terminal normal secretin (T. N. S.) was weaker than the normal secretin, being extracts made respectively from dogs which had died a lingering protracted death over twelve to eighteen hours, on the one hand, and from lively animals killed during health, on the other. In our earlier work, and in the work of the few others who have attempted such observations, comparisons were made between the secretin from human beings who had died "slowly," as is generally the case with hospital subjects, and that from dogs recently killed as recorded.

We seem to have here illustrated, therefore, one of the factors which may be, and doubtless are, operative to prevent or hamper the detection of prosecretin in the diseased human subject. The effect of a lingering death is apparently to make the prosecretin content of the duodenum less easy of extraction and perhaps the mucosa less active, as contrasted with freshly killed animals.

We have made a few observations on the nature of the pancreatic juice which is secreted at various periods during a flow, and tests of its amylolytic power indicate very clearly that, while the juice becomes weaker as it is poured out in larger and larger quantities over long periods, it preserves this one ferment action at least to a very significant degree.

This question, however, is almost one by itself and requires special work devoted to it, but the presumption is all in favor of the view that the other ferments of the juice are also present.

#### CONCLUSIONS

1. The removal of the suprarenal glands induces in dogs a flow of pancreatic juice. This has been equaled in duration and activity only by the processes, natural or experimental, which depend on activation by duodenal secretin.

2. Taken in connection with the inhibitory action of suprarenal and pituitary extracts on the pancreatic flow, this suggests a control over the pancreas, by the adrenals at least, in the absence of which the gland secretes more actively.

3. This activation of the pancreas may occur with a high systemic blood-pressure, though it generally occurs when the systemic blood-pressure is relatively low. Hemorrhage may modify or prevent it.

4. There is some evidence to indicate that on the death of a dog from removal of the adrenals, there is present in the duodenum more prosecretin than exists in dogs otherwise operated on which have their adrenals intact, and which die after a comparable long period of etherization. This preponderance may be a contributory factor in the production of a flow.

5. One of the factors which seem to make detection of prosecretin in human beings difficult is probably the lingering death of most of those from whom the intestinal extracts are made. In clinical investigations of secretin comparisons should not be made between such preparations and those from freshly killed animals, unless this fact be borne in mind.

#### PROTOCOLS

The following records are abstracts of our experiments, and are for the most part self-explanatory. The first column indicates the time, either directly or in terms of the intervals between the events recorded. The second column indicates the flow of pancreatic juice, in terms of cannulas or divisions of the cannula.

The same cannula was used practically throughout and contained ninety divisions. Occasionally we failed to record when it was exactly full, the excess being generally estimated on the ungraded distal end.

The last column indicates the blood-pressure in millimeters of mercury. The records of the secretin injections show the pancreatic output in terms of cannulas and fractions of a cannula, the latter giving the actual divisions reached.

The table below indicates the observations on which we based our first report<sup>1</sup> in May, 1909. They were on animals fed at various periods before the operation, in most of whom digestion was taking place more or less rapidly. We were assisted in making these observations by Dr. Stone and Dr. Rulon, then of the fourth-year class in the Medical School of the University of Pennsylvania.

Finally, we wish to express our obligation to Dr. Edward T. Reichert for the facilities he has placed at our command which have made possible the observations and studies here recorded. We also desire again to thank Dr. David L. Edsall for the kindly interest and encouragement which have aided us so materially in all our work.



## OBSERVATIONS WHICH FORMED THE BASIS OF THE FIRST REPORT

## PERSONALLY CONDUCTED OBSERVATIONS

Normal dogs	Dogs from which the adrenals had been removed
O T O+(!)T O	+ + (!) T +

## OBSERVATIONS CONDUCTED CHIEFLY BY DR. STONE AND DR. RULON

O	+ + +
---	-------

O = no flow.

T = no "terminal" flow.

(!) = a violent flow in the instance immediately preceding it.

+ = a well-marked flow.

## SUMMARY OF RESULTS OF PRESENT WORK

Normal control with flow.....	0
Normal control with no flow.....	6
Adrenals out with flow.....	9
Adrenals out with no flow.....	0
One adrenal out with flow; 1, violent; 1, marked (worms and blood in duodenum); 2, slight; 1, moderate; total.....	5
One adrenal out with no flow.....	4
One adrenal out; failure (clot in cannula).....	3
Abdominal injury with flow (chyme in intestine).....	1
Abdominal injury with no flow.....	1
Adrenals out; early death with flow.....	5
Adrenals out; early death with no flow.....	6
One adrenal out; early death with no flow.....	1
Total .....	38

## GROUP 1.—NORMAL CONTROLS

*Experiment 1, Dec. 29, 1909: Normal Dog, No Flow*

	Ether.	Flow Active (9 Hours).	Blood-pressure.
9:45 a. m.	83 min. later	first cannula full	148
1:05 p. m.	1 hr. 49 sec. later	second cannula full	80
	2 hr. 20 min. later	third cannula full	70
4:01 p. m.	1 hr. 24 min. later	fourth cannula full	80
	1 hr. 17 min. later	fifth cannula full	*75
			*45
6:09 p. m.	27 min. later	flow	40
	6 min. later	sixth cannula full	20
	19 min. later	80 divisions	16
6:34 p. m.	Death.		

\* Fluctuation of blood-pressure with each systole.

Considerable congestion. Spleen small, but rather dark blue. Other organs not congested. Stomach and duodenum empty. Intestines show some stasis, but not nearly so great perhaps as some dogs show with adrenals removed. Intestines used for secretin.

*Experiment 2, Jan. 3, 1910: Normal, No Flow, 36 hr. Fast*

			Blood-pressure.
9:20 a. m.	Ether.		78
	1 hr. 27 min. later	first cannula full	90
	1 hr. 42 min. later	second cannula full	94
	51 min. later	third cannula full	86
	41 min. later	fourth cannula full	80
	35 min. later	fifth cannula full	78
	43 min. later	sixth cannula full	66
4:33 p. m.	36 min. later	seventh cannula full	60
	36 min. later	eighth cannula full	66
	33 min. later	ninth cannula full	64
	30 min. later	tenth cannula full	50
	26 min. later	eleventh cannula full	clot
7:34 p. m.	30 min. later	twelfth cannula full	36
7:53 p. m.	19 min. later	64 divisions.	death

Blood-pressure was low and early became low for a normal dog, indicating some analogy to the condition after long etherization or removal of adrenals. Intestine very slightly congested. Spleen markedly so in areas. Stomach and intestine alkaline in reaction.

*Experiment 3, Jan. 13, 1909: Normal Dog, No Flow*

			Blood-pressure.
9:30 a. m.	Ether.		180
	4 hr. 12 min. later	first cannula full	154
3:30 p. m.	2 hr. 16 min. later	second cannula full	160
5:14 p. m.	1 hr. 28 min. later		120
	1 hr. 03 min. later	third cannula full	136
	1 hr. 30 min. later	fourth cannula full	105
	1 hr. 12 min. later	fifth cannula full	53
	1 hr. 20 min. later	sixth cannula three	108
	59 min. later	seventh cannula three	80
	45 min. later	eighth cannula three	70
	18 min. later	69 divisions	Death.

Typical nutmeg liver. Apparently respiratory death after 14 hours. Death somewhat sudden.

*Experiment 4, Feb. 24, 1910: Normal Dog, No Flow*

			Blood-pressure.
9:37 a. m.	Drum starts		136
12:15 p. m.	35½ divisions.		134
	Sucked out as cannula was removed and replaced.		
	thinking the duct possibly blocked. O. K., however.		
4:01 p. m.	28 divisions		130
4:53 p. m.			104
6:39 p. m.	31 divisions		108
7:40 p. m.	Cannula taken out and replaced for the second time.		
	O. K., however; cannula emptied.		
	28 divisions		
9:23 p. m.	43 divisions		94
9:57 p. m.	44 divisions		92

Blood-pressure.

Blood-pressure actually much lower as, owing to an unrecognized clot, it had not fallen and went no lower, even at death.

10:27 p. m.      Death      90

Duct clear. Pancreas appeared normal. Intestines congested where handled, otherwise normal. Stomach empty and contracted. Spleen mottled, not bullous. Liver and kidneys show fatty degeneration. Lungs not collapsed. Anthracotic heart greatly hypertrophied. Adrenals very hemorrhagic.

*Experiment 5, Feb. 28, 1910: Normal Dog, No Flow*

			Blood-pressure.
9:05 a. m.	Ether.		134
10:43 a. m.		first cannula full	136
1:41 p. m.	2 hr. 48 min. later	second cannula full	144
3:55 p. m.		third cannula full	136
	1 hr. 32 min. later	fourth cannula full	110
7:04 p. m.	1 hr. 37 min. later	fifth cannula full	106
8:46 p. m.	1 hr. 53 min. later	sixth cannula full	106
9:40 p. m.	56 min. later	seventh cannula full	82
10:30 p. m.	52 min. later	eighth cannula full	60
11:31 30 sec.	52 min. later	ninth cannula full	60
12:00 p. m.	30 min. later	tenth cannula full	42
12:27 a. m.	29 min. later	eleventh cannula full	42
1:01 a. m.	36 min. later	twelfth cannula full	46
1:42 a. m.	41 min. later	thirteenth cannula full	28
1:48 a. m.	7 min. later	30 divisions.	death

Experiment lasted 17 hours.

Liver shows fatty change and some nutmeg appearance. Duct clear. Intestines empty and not congested. Stomach empty.

*Experiment 6, April 8, 1910: Normal Control, No Flow*

		Blood-pressure.
9:30 a. m.	Ether.	
9:53 a. m.	Tracing began.	146
1:02 p. m.	No flow	120
3:45 p. m.	No flow	120
5:50 p. m.	No flow	106
7:54 p. m.	No flow	114
9 p. m.	No flow	116
10:49 p. m.	No flow	76
12:13 a. m.	More ether given	108
12:40 a. m.	No flow	58
1 a. m.	No flow	46
1:14 a. m.	Death.	

This dog might have lived many hours yet, as blood-pressure was 108 at midnight; therefore, as the artificial condition of etherization was desired, and no ether had been given for some time except in small amounts, it was added until the blood-pressure fell. Otherwise the observation would have been equivalent to watching a healthy normal dog indefinitely.

Liver not congested. Spleen contracted, normal in color. Duct clear. Stomach empty. Adrenals, distinctly large for a dog of this size (Fox-terrier bitch), show a brown liquid medulla, hemorrhagic junction of medulla and cortex and lighter periphery to cortex. Intestines empty, not congested.

## GROUP 2.—BOTH ADRENALS REMOVED\*

*Experiment 7, Dec. 15, 1909: Adrenals Out and Flow*

	Ether		Blood-pressure.
11:40	L.A.O.		96
11:58	1 hr. 26 min. later	first cannula full	100
	38 min. later	second cannula full	96
	47 min. later	third cannula full	108
	1 hr. 50 min. later	fourth cannula full	78
	1 hr. 9 min. later	fifth cannula full	48
	20 min. later	sixth cannula full	†54
	14 min. later	seventh cannula full	42
	4 min. later	eighth cannula full	46
2 min.	30 sec. later	ninth cannula full	46
	3 min. later	tenth cannula full	46
	4 min. later	eleventh cannula full	42
	6 min. later	twelfth cannula full	44
	11 min. later	thirteenth cannula full	44
	10 min. later	fourteenth cannula full	clot
	6 min. later	fifteenth cannula full	50
5 min.	30 sec. later	sixteenth cannula full	50
	6 min. later	seventeenth cannula full	50
	5 min. later	eighteenth cannula full	50
	5 min. later	nineteenth cannula full	50
4 min.	30 sec. later	twentieth cannula full	46
	5 min. later	twenty-first cannula full	42
4 min.	30 sec. later	twenty-second cannula full	38
	3 min. later	twenty-third cannula full	34
	2 min. later	twenty-fourth cannula full	34
	1 min. 50 sec. later	twenty-fifth cannula full	34
	1 min. 50 sec. later	twenty-sixth cannula full	30
	2 min. 50 sec. later	twenty-seventh cannula full	26

7:23 p. m. Death. Stomach and intestines free from food.

Time of removal of right adrenal inadvertently omitted.

\* R.A.O.=Right adrenal out. L.A.O.=Left adrenal out. S.O.=“Sucked out”=cannula emptied and record begins anew.

† 5:35 p. m.

*Experiment 8, Dec. 20, 1909: Adrenals Removed; Flow*

			Blood-pressure.
10:40 a. m.	Tracing begun: forty-eight-hour fast		110
10:48 a. m.	R.A.O.		
11:08 a. m.	L.A.O.		
11:10 a. m.	Juice at 77		
	12 min. later	first cannula full	90
	1 hr. 41 min. later	second cannula full	96
	1 hr. 16 min. later	third cannula full	90
2:30 p. m.	17 min. later		
	1 hr. 16 min. later	fourth cannula full	80
	1 hr. 19 min. later	fifth cannula full	70
	30 min. later	sixth cannula full; flow began	66
	11 min. later	seventh cannula full	66
	8 min. 30 sec. later	eighth cannula full	70

			Blood-pressure.
	9 min. later	ninth cannula full	74
	9 min. later	tenth cannula full	76
	7 min. 30 sec. later	eleventh cannula full	76
	8 min. 30 sec. later	twelfth cannula full	76
	9 min. 30 sec. later	thirteenth cannula full	80
	12 min. later	fourteenth cannula full	82
	15 min. later	fifteenth cannula full	82
	18 min. later	sixteenth cannula full	82
	21 min. later	seventeenth cannula full	90
	1 hr. 13 min. later *	eighteenth cannula full	50
	56 min. later	15 divisions	
10:00 p. m.		death	

Cannula probably O. K. Stomach acid, brown fluid; no congestion. Spleen congested; liver not.

\* Then S. O. to 52.

*Experiment 9, Dec. 22, 1909: Adrenals Out, with Flow\**

10:30 a. m.	Ether begins		
10:48 a. m.	R.A.O.		
11:08 a. m.	L.A.O.		
11:22 a. m.	Drum starts		
			Blood-pressure.
11:27 a. m.		cannula full	134
	1 hr. 6 sec. later	first cannula full	120
	1 hr. 7 sec. later	second cannula full	102
	1 hr. 39 min. later	third cannula full	92
	53 min. later	fourth cannula full	66
	30 min. later	fifth cannula full	49
	12 min. later	sixth cannula full	46
	11 min. later	seventh cannula full	46
	4 min. later	eighth cannula full	46
	3 min. 30 sec. later	ninth cannula full	44
	3 min. 30 sec. later	tenth cannula full	clot
	4 min. later	eleventh cannula full	32
6:06 p. m.		death	

\* Operative procedures in following order: Adrenals out, cannula in pancreas, respiratory cannula, blood-pressure.

Small amount of ether apparently caused death. Spleen bullous and very congested. Liver moderately congested. Kidneys moderately congested. Intestines greatly congested and almost black in upper part of duodenum. Intestines and stomach empty, and alkaline or neutral.

*Experiment 10, Jan. 6, 1910: Adrenals Out with Flow, but Early Death*

9:45 a. m.	R.A.O.		
10:00 a. m.	L.A.O.		
10:18 a. m.	Drum starts.		
			Blood-pressure.
10:25 a. m.			88
	2 hr. 9 min. later	first cannula full	40
	24 min. later	second cannula full	20
	17 min. later	third cannula full	20
	8 min. 30 sec. later	fourth cannula full	20
	8 min. 30 sec. later	fifth cannula full	20
Death.	22 min. later	55 divisions	

Much bile extruded. Intestines and liver not much congested. Spleen considerably congested. Stomach alkaline. Stomach empty, except for bile and a plum-stone.

*Experiment 11, Jan. 10, 1910: Adrenals Removed, Moderate Flow, Early Death*

Cannula in bile-duct.

9:20 a. m.	Ether		
9:40 a. m.	R. A. O.		
9:48 a. m.	L. A. O.		
			Blood-pressure.
10:22 a. m.	Drum starts		124
	31 min. later	first cannula full	114
	42 min. later	second cannula full	100
	Fall of blood-pressure from manipulation of intestines to replace bile-duct		44
	31 min. later	fourth cannula full	28
	18 min. 30 sec. later	fifth cannula full	16
	7 min. 30 sec. later	sixth cannula full	10

1:06 p. m. Death

Spleen greatly congested, though not bullous. Stomach somewhat congested and considerable bile. Liver moderately congested. Intestines locally hemorrhagic where handled and somewhat darkened throughout. Twelve c.c. bile altogether. No flow of bile at end.

*Experiment 12, Jan. 11, 1910: Adrenals Removed, with Flow*

			Blood-pressure.
9:38 a. m.	Ether		
10:08 a. m.	R. A. O.		146
10:18 a. m.	L. A. O.		104
	32 min. later	first cannula full	
	16 min. later	second cannula full	110
	50 min. later	third cannula full	120
	25 min. later	fourth cannula full	124
	30 min. later	fifth cannula full	112
	32 min. later	sixth cannula full	102
	25 min. later	seventh cannula full	90
	20 min. later	eighth cannula full	80
	24 min. later	ninth cannula full	80
	22 min. later	tenth cannula full	70
	10 min. later	eleventh cannula full	clot
	9 min. later	twelfth cannula full	60
	8 min. 30 sec. later	thirteenth cannula full	60
	6 min. later	fourteenth cannula full	50
	2 min. 30 sec. later	fifteenth cannula full	44
	2 min. 30 sec. later	sixteenth cannula full	44
	4 min. later	seventeenth cannula full	44
	5 min. later	eighteenth cannula full	44
	4 min. later	nineteenth cannula full	44
	3 min. later	twentieth cannula full	40
	2 min. 15 sec. later	twenty-first cannula full	40
	1 min. 45 sec. later	twenty-second cannula full	34
	1 min. 30 sec. later	twenty-third cannula full	34
	1 min. 15 sec. later	twenty-fourth cannula full	
	1 min. 15 sec. later	twenty-fifth cannula full	30
	1 min. later	twenty-sixth cannula full	30

## Blood-pressure.

50 sec. later twenty-seventh cannula full	30
40 sec. later twenty-eighth cannula full	24
32 sec. later twenty-ninth cannula full	24
36 sec. later thirtieth cannula full	24
30 sec. later thirty-first cannula full	22
30 sec. later thirty-second cannula full	20
1 min. 10 sec. later thirty-third cannula full	20
3 min. later thirty-fourth cannula full	14

4:00 p. m. Death.

Liver not congested. Spleen moderately congested; very dark. Stomach empty; slight amount of chyme. No congestion of intestines anywhere, except at a few spots opposite cannula where handled. No flow of bile to speak of.

*Experiment 13, Feb. 3, 1910: Adrenals Removed; Flow*

## Blood-pressure.

9:45 a. m.	L. A. O.		
9:53 a. m.	R. A. O.		
10:14 a. m.	Drum starts		130
	50 min. later	first cannula full (overflow)	132
	41 min. later	second cannula full	138
	12 min. later	third cannula full	140
	14 min. 30 sec. later	fourth cannula full	130
	15 min. later	sixth cannula full (overflow)	132
	4 min. later	seventh cannula full	126
	5 min. 30 sec. later	eighth cannula full	126
	6 min. later	ninth cannula full	112
	9 min. later	tenth cannula full	110
	4 min. 30 sec. later	eleventh cannula full	102
	4 min. 30 sec. later	twelfth cannula full	98
	4 min. later	thirteenth cannula full	104
	4 min. later	fourteenth cannula full	90
	4 min. 30 sec. later	fifteenth cannula full	90
	4 min. 30 sec. later	sixteenth cannula full	86
	6 min. later	seventeenth cannula full	84
	7 min. later	eighteenth cannula full	88
	3 min. later	nineteenth cannula full	86
	3 min. 55 sec. later	twentieth cannula full	80
	5 min. 30 sec. later	twenty-first cannula full	76
	7 min. later	twenty-second cannula full	70
	5 min. 10 sec. later	twenty-third cannula full	72
	22 min. later	twenty-fourth cannula full	Death.

Position of blood-pressure above base line somewhat doubtful. Autopsy shows nothing of importance. Spleen shows very small areas of extreme congestion. Intestines show hemorrhagic congestion at edges of folds in that area which was subjected to handling.

*Experiment 14, April 4, 1910: Adrenals Removed; Moderate Flow*

## Blood-pressure.

10:25 a. m.	R. A. O.		
10:35 a. m.	L. A. O.		
10:58 a. m.	Drum starts		
	28 min. later	juice flowing O. K.	
	11 min. later	first cannula full	130
	6 min. 30 sec. later	second cannula full	128

		Blood-pressure.
	11 min. later	third cannula full 132
	23 min. later	fourth cannula full 104
	43 min. later	fifth cannula full 102
	13 min. 30 sec. later	sixth cannula full 104
	3 min. later	seventh cannula full 112
	9 min. 30 sec. later	eighth cannula full 104
	7 min. later	ninth cannula full 104
	29 min. later	tenth cannula full 98
	43 min. later	eleventh cannula full (overflow) 92
	11 min. later	twelfth cannula full 82
	8 min. 30 sec. later	thirteenth cannula full 78
	42 min. later	fourteenth cannula full 62

4:00 p. m. Death.

Autopsy showed no congestion of intestine. A small clot was found in opening of cannula, possibly partially occluding the duct.

*Experiment 15, Feb. 8, 1910: Adrenals Removed; Hemorrhage; Flow*

		Blood-pressure.
9:50 a. m.	R. A. O.	
10:10 a. m.	L. A. O.	
10:25 a. m.	Drum starts	160
	1 hr. 51 min. later	first cannula full 114
	1 hr. 8 min. later	second cannula full 102
	1 hr. 40 min. later	third cannula full 62
	15 min. later *	fourth cannula full 60
	3 min. 30 sec. later	fifth cannula full 60
	3 min. 30 sec. later	sixth cannula full 60
	3 min. later	seventh cannula full 64
	3 min. 30 sec. later	eighth cannula full 72
	3 min. 10 sec. later	ninth cannula full 70
	3 min. 50 sec. later	tenth cannula full 64
	4 min. later	eleventh cannula full 64
	5 min. 10 sec. later	twelfth cannula full 64
3:54 p. m.	13 min. 30 sec. later	thirteenth cannula full at 70th division

Death.

\* Flow begins 3 p. m.

Stomach empty, except for a little bile, as are also the intestines. Pancreas paler than normal. Duct clear and free, extensive hemorrhage in abdomen; few clots; no congestion of intestine and stomach, except for a few spots on the intestines where handled. Blood in abdomen probably 25 per cent. of total blood or more. No supernatant serum. Liver normal in color. No terminal flow. Spleen blue and slightly roughened; rather hard and apparently not swollen. Kidneys not so blue as usual. Apparently no general congestion; little, if any, anywhere.

*Experiment 16, Feb. 12, 1910: Adrenals Removed and Flow*

		Blood-pressure.
9:50 a. m.		150
10:25 a. m.	R. A. O.	
10:40 a. m.	L. A. O.	76
11:29 a. m.		first cannula full 76
12:04 p. m.	35 min. later	second cannula full 76
12:30 p. m.	26 min. later	third cannula full 70
12:51 p. m.	21 min. later	fourth cannula full 70



		Blood-pressure.
1:11:30 p. m.	20 min. 30 sec. later fifth cannula full	50
1:30 p. m.	18 min. 30 sec. later sixth cannula full	44
1:43 p. m.	13 min. later seventh cannula full	40
1:48 p. m.	5 min. later eighth cannula full	36
1:49:10 p. m.	1 min. 10 sec. later ninth cannula full	36
1:50:30 p. m.	1 min. 20 sec. later tenth cannula full	36
1:51:18 p. m.	48 sec. later eleventh cannula full	34
1:52:13 p. m.	55 sec. later twelfth cannula full	30
1:55:8 p. m.	55 sec. later thirteenth cannula full	30
1:53 p. m.	at 79th division.	Death.

*Experiment 17, Feb. 17, 1910: Adrenals Removed; Flow*

		Blood-pressure.
9:50 a. m.		136
10:11 a. m.	R. A. O.	
10:32 a. m.	L. A. O.	
10:57 a. m.		
11:34 a. m.		86
11:46 a. m.		96
1:38 p. m.	first cannula full	90
1:42 p. m.	second cannula full	84
1:44:30 p. m.	third cannula full	90
1:51:30 p. m.	fourth cannula full	86
1:55:30 p. m.	fifth cannula full	84
2:02 p. m.	sixth cannula full	80
2:05 p. m.	seventh cannula full	78
2:07:30 p. m.	eighth cannula full	80
2:15:30 p. m.	ninth cannula full	80
2:26 p. m.	tenth cannula full	70
2:41:30 p. m.	eleventh cannula full	70
2:44:30 p. m.	twelfth cannula full	66
2:48:30 p. m.	thirteenth cannula full	64
2:57:30 p. m.	fourteenth cannula full	52
2:59 p. m.	fifteenth cannula full	56
3:05 p. m.	sixteenth cannula full	54
3:18 p. m.	seventeenth cannula full	*46
3:47:30 p. m.	eighteenth cannula full	44
4:02:30 p. m.	nineteenth cannula full	42
	Death.	

\* Ether added and it rises to 100.

Three hundred c.c. blood-stained fluid in peritoneum. Duct clear. Spleen moderately congested. Liver more congested. Intestines hemorrhagic high up.

GROUP 3.—ADRENALS REMOVED: EARLY DEATH

*Experiment 18, Dec. 13, 1910: Adrenals Removed and Flow.*

No mention by accident of time of removal of left adrenal.

		Blood-pressure.
9:30 a. m.	Ether	150
9:47 a. m.	R. A. O.	
	48 min. later first cannula full	86
	48 min. later second cannula full	50
	17 min. later third cannula full	22

		Blood-pressure.
	* 2 min. 40 sec. later fourth cannula full	18
	5 min. later fifth cannula full	
12:10 p. m.	Death.	
	* Violent flow.	

Fasted twenty-four hours, but stomach contained small amount of water and very small amount of food. Duodenum deeply congested. Intestine contained chyme throughout entire length.

*Experiment 19, Dec. 17, 1909: Adrenals Removed; Early Death; No Flow*

		Blood-pressure.
9:58 a. m.	R. A. O.	
10:03 a. m.	L. A. O.	
10:24 a. m.	Drum starts	110
	1 hr. 22 min. later death	98

Slight flow during that time, but no cannula filled.

*Experiment 20, Dec. 18, 1910: Adrenals Removed; Hemorrhage; No Flow; Early Death*

		Blood-pressure.
9:48 a. m.	R. A. O.	variable 104 to 130
9:59 a. m.	L. A. O.	hemorrhage from neck 80
	1 hr. 14 min. later first cannula full, S. O. to 10	32
	Very long cannula, not generally used.	
	37 min. later cannula 14 divisions.	Death.

Intestine, spleen, liver and kidneys deeply congested. Pancreas not congested. Right adrenal broken in removal.

*Experiment 21, Feb. 2, 1910: Adrenals Removed; Early Death, but yet a Flow*

		Blood-pressure.
9:30 a. m.	Ether	
9:45 a. m.	R. A. O.	
9:53 a. m.	L. A. O.	
10:12 a. m.	Drum starts	110
	1 hr. 9 min. later first cannula full	94
	50 min. later second cannula full	20
	3 min. 30 sec. later third cannula full	clot
	2 min. 30 sec. later fourth cannula full	clot
12:20 p. m.	6 min. later fifth cannula full	Death.

Stomach full of bile and some hair. Spleen blue, but not unduly congested. Intestines empty and not congested. Liver not congested.

*Experiment 21, Feb. 7, 1910: Adrenals Removed; No Flow; Early Death.*

		Blood-pressure.
10:00 a. m.	Ether	
10:14 a. m.	R. A. O.	
10:21 a. m.	L. A. O.	
10:50 a. m.	Drum starts	94
	Both adrenals torn in removal.	
	35 min. later first cannula full	92
	52 min. later second cannula full	28
	25 min. later third cannula full	Death.

*Experiment 23, Feb. 7, 1910: Adrenals Removed; Hemorrhage; No Flow*

Blood-pressure.

1:30 p. m.	R. A. O.		
1:37 p. m.	L. A. O.		
2:00 p. m.	Drum started		150
	2 hrs. 14 min. later	first cannula full	130
	1 hr. 25 min. later	second cannula full	40
	1 hr. 5 min. later	80th division	Death.

Much hemorrhage in abdomen. No congestion. No flow.

*Experiment 24, Feb. 10, 1910: Adrenals Removed; Slight Flow; Early Death*

Blood-pressure.

9:45 a. m.	Ether		
10:00 a. m.	R. A. O.		
10:06 a. m.	L. A. O.		
10:25 a. m.	Drum starts		130
	7 min. later	hemorrhage from neck, about 4 ounces	110
	3 min. later		126
	45 min. later	dog vomits bile, insufflates and nearly dies; when quiet again blood-pressure	110
	41 min. later	first cannula full	84
	29 min. later	second cannula full	64
	11 min. later	third cannula full	54
	9 min. later	55th division	Death.

Pancreatic cannula free. Lungs do not collapse on opening thorax.

*Experiment 25, Feb. 11, 1910: Adrenals Removed; Early Death; No Flow*

Blood-pressure.

9:35 a. m.	R. A. O.		
9:44 a. m.	L. A. O.		
10:14 a. m.	Drum starts		94
	1 hr. 40 min. later	first cannula full	50
	42 min. later	85th division	Death.

Stomach and intestines empty except for bile. Duct clear. Spleen only slightly congested. Intestines much congested everywhere and hemorrhagic in spots throughout. Death too early.

*Experiment 26, Feb. 15, 1910: Adrenals Removed; Hemorrhage; No Flow; Early Death*

Blood-pressure.

9:27 a. m.	Ether		180
9:54 a. m.	R. A. O.		
10:03 a. m.	L. A. O.		136
	1 hr. 9 min. later	40 divisions previously S. O.	100
12:24 p. m.	1 hr. 10 min. later	first cannula full	86
1:30 p. m.	1 hr. 7 min. later	second cannula full	74
2:41 p. m.	1 hr. 5 min. later	third cannula full	34
2:50 p. m.	12 min. later	78th division.	Death.

Five hundred c.c. blood in peritoneal cavity, evidently from the site of right adrenal.

## GROUP 4.—LEFT ADRENAL REMOVED

*Experiment 27, March 11, 1910: Left Adrenal Removed; Moderate Flow*

		Blood-pressure.
9:30 a. m.	Tracing began; adrenal torn in removal	150
9:35 a. m.	L. A. O.	
10:31 a. m.		130
	Juice flowing freely from start.	
11:16 a. m.	first cannula full (100)	120
12:50 p. m.	second cannula full	126
1:59 p. m.	third cannula full	120
2:50 p. m.	fourth cannula full	124
3:09 p. m.	fifth cannula full	80
3:32 p. m.	sixth cannula full	96
3:44 p. m.	seventh cannula full	82
4:01 p. m.	eighth cannula full	92
4:17 p. m.	ninth cannula full	84
4:31 p. m.	tenth cannula full	64
4:43 p. m.	eleventh cannula full	40
4:55:30 p. m.	twelfth cannula full	30
5:12 p. m.	thirteenth cannula full	Death.

Some flow all day. Duct contained a small soft loose clot. Pancreas not congested. Moderate amount of blood-stained fluid in abdomen. Spleen very blue and congested, but smooth. Stomach and intestines full of bile, but no food. Slight congestion where handled. Liver somewhat fatty, but not congested. Left adrenal shows striation and hemorrhage in cortex. Medulla soft and relatively empty.

*Experiment 28, March 14, 1910: Left Adrenal Removed; Slight Flow*

		Blood-pressure.
9:10 a. m.	Ether	184
9:33 a. m.	L. A. O.	126
11:24 a. m.	first cannula full	158
2:26 p. m.	second cannula full (overfull)	136
3:03 p. m.	B. P. cannula blows out and 50 c.c. blood lost	136
3:26 p. m.	third cannula full	146
4:43 p. m.	fourth cannula full	128
5:52 p. m.	fifth cannula full (overfull)	84
6:37 p. m.	sixth cannula full	64
7:22:30 p. m.	seventh cannula full	52
8:04 p. m.	eighth cannula full	50
8:35 p. m.	ninth cannula full	26
8:43 p. m.	43d division.	Death.

This dog evidently died of heart failure. Intestines extremely congested throughout entire extent. In part the mucosa was hemorrhagic. Spleen dark blue. Pancreatic cannula clear. Pancreas showed no evidence of congestion. Right adrenal was grayish pink, shows hemorrhagic striation on section. Lungs normal. Heart flabby. Liver congested. Stomach and intestines empty, save for bile and possibly some chyme in lower part of small intestine.

*Experiment 29, March 16, 1910: Left Adrenal Removed; Some Flow*

		Blood-pressure.
9:35 a. m.	Ether	156
10:00 a. m.	L. A. O.	
10:20 a. m.		144
12:30 a. m.		113
	Fluid in cannula at 80 sucked out on account of blood-stain; blood-pressure pen slipped down on piston-rod	
		138
4:01 p. m.	first cannula full	126
5:19 p. m.	second cannula full	92
6:10 p. m.	third cannula full	78
6:55 p. m.	fourth cannula full	70
7:26 p. m.	fifth cannula full (95)	66
7:58 p. m.	sixth cannula full	68
8:24 p. m.	seventh cannula full	68
8:50 p. m.	eighth cannula full	clot
	(at 100 overfull)	
9:06:30 p. m.	ninth cannula full	40
9:20 p. m.	cannula at 85	Death.

Juice clear for at least three hours and flowing steadily and progressively slightly faster. It was very slow in morning. One hundred c.c. blood in abdomen, including a good-sized clot, evidently the site of the left adrenal. Retroperitoneal fat tissue shows hemorrhage into its substance. Liver shows some fatty and possibly some nutmeg appearance. Small clot in pancreatic duct which does not occlude duct or mouth of cannula. Pancreas normal in color. Intestines intensely hemorrhagic where handled. Stomach contains mucus and hair. Intestines full of a queer gruel-like mass, color of digested blood, which may be the gastric contents in part. Spleen moderately congested and smooth. Right adrenal shows area of hemorrhage on inside edge of cortex all around it.

*Experiment 30, March 17, 1910: Left Adrenal Removed; No Flow*

		Blood-pressure.
At start		170
10:26 a. m.	L. A. O.	
12:05 p. m.		120
2:26 p. m.		120
5:55 p. m.	first cannula full	106
7:05 p. m.		100
11:20 p. m.	87th division	Death.

Dog's death at 11:20 hastened by ether. Only one cannula in thirteen hours. Bloody all day, however. Liver not congested. Spleen moderately so. Stomach and intestines empty, except for bile. Pancreas pale. Cannula clear below joint. Duct seems clear. Moderate amount of blood-stained fluid in abdomen. Right adrenal in better shape than most. But little injection around the cortex.

This dog was another instance of a practically normal dog which might have lived many hours yet.

*Experiment 31, March 28, 1910: Left Adrenal Removed; Big Flow*

		Blood-pressure.
9:30 a. m.	Ether	
9:42 a. m.	L. A. O.	174
11:33 a. m.	cannula 25	150
12:37 p. m.		176

		Blood-pressure.
2:53 p. m.		164
3:34 p. m.	first cannula full	170
4:36 p. m.	second cannula full (97)	154
5:09 p. m.	third cannula full	160
5:33 p. m.	fourth cannula full	160
5:57 p. m.	fifth cannula full (overflow)	136
6:10 p. m.	sixth cannula full	134
6:15 p. m.	seventh cannula full	130
6:24 p. m.	eighth cannula full	120
	6 min. 30 sec. later ninth cannula full	clot
	5 min. 30 sec. later tenth cannula full	clot
	5 min. 20 sec. later eleventh cannula full	clot
	5 min. later twelfth cannula full	clot
	Roll changed thirteenth cannula full	clot
	5 min. later fourteenth cannula full	clot
	5 min. 30 sec. later fifteenth cannula full	clot
	7 min. later sixteenth cannula full *	
7:18:30 p. m.	5 min. later seventeenth cannula full	44
	2 min. 20 sec. later eighteenth cannula full	44
	4 min. later nineteenth cannula full	40
7:29 p. m.	4 min. later 79th division	Death.

\* Loss of juice as cannula came out; loss of 20 divisions.

Small amount of blood-stained fluid in abdomen. Stomach and intestines not congested. Intestines contain small amount of yellow grumous material, which was possibly chyme. Stomach contains considerable quantity of green, muddy fluid. Spleen not congested, save for a few bullae. Kidneys congested. Right adrenal very much congested, especially at junction of cortex and medulla. Lungs and heart normal.

Right adrenal, parathyroids and pituitary taken for sections.

*Experiment 32, March 29, 1910: Left Adrenal Removed; No Flow*

		Blood-pressure.
9:30 a. m.	Ether	130
10:00 a. m.	L. A. O.	
11:23 a. m.	no flow	136
12:50 p. m.	no flow	128
1:55 p. m.	no flow	110
3:22 p. m.	no flow	90
4:30 p. m.	Death	60

Very little fluid in abdomen which pushed intestines into flank. Upper portion of duodenum very hemorrhagic. Intestines, in fact, very deeply congested throughout. Spleen very dark blue and covered with bullae. No clot in duct. Liver congested; kidneys very much so. Stomach empty, except for air and some bloody, bile-stained mucus. Intestines empty, except for considerable blood. Right adrenal quite congested and blue, especially medulla. Cortex only slightly so. Left adrenal, removed in morning, also shows some cyanosis of the medulla. Heart very dilated and collapsed. Lungs normal.

GROUP 5.—RIGHT ADRENAL REMOVED

*Experiment 33, Feb. 26, 1910: Attempt to Cause Abdominal Trauma Analogous to Removal of Both Adrenals; No Flow*

		Blood-pressure.
9:05 a. m.	Ether	
9:19 a. m.	R. A. O.	142

			Blood-pressure.
9:25 a. m.		pancreatic cannula in place	
	3 hrs. 18 min. later	first cannula full	142
1:43 p. m.	1 hr. 7 min. later	second cannula full	116
	34 min. later	third cannula full	94
	39 min. later	fourth cannula full	82
	About 5 minutes before last entry blood-pressure fell to 42, probably from too much ether.		
	23 min. later	fifth cannula full	58
	21 min. later	sixth cannula full	56
	16 min. later	seventh cannula full	46
4:05 p. m.	12 min. 30 sec. later	81st division	Death.

Duct clear. This dog gave a more than usually active flow at start. Spleen shows a few bullous patches; not especially congested. Liver slightly congested. Intestines very slightly congested and full of hemorrhagic ulcers in the upper part. Stomach contains considerable bile. Right adrenal was considerably torn in removal and was friable.

*Experiment 34, March 2, 1910: One Adrenal Out; Early Death; No Flow*

			Blood-pressure.
9:10 a. m.	Ether		166
9:30 a. m.	R. A. O.		
9:51 a. m.			120
12:00 m.	2 hrs. 6 min. later	dog dies from sudden respiratory failure.	

*Experiment 35, March 3, 1910: Attempt to Get Flow by Abdominal Injury; No Flow\**

			Blood-pressure.
9:49 a. m.			174
10:02 a. m.	R. A. O.		
10:10 a. m.			136
11:44 a. m.		first cannula full	145
12:47 p. m.		second cannula full	145
1:39 p. m.		third cannula full	130
2:47 p. m.		fourth cannula full	120
3:56 p. m.		fifth cannula full	92
5:00 p. m.		sixth cannula full (100)	94
6:04 p. m.		seventh cannula full (105)	78
6:30 p. m.		eighth cannula full (105)	64
7:27 p. m.		ninth cannula full	44
8:39 p. m.		tenth cannula full	40
9:15 p. m.		cannula at 57	Death.

\* R. A. O. for control of flow.

Duct free. Stomach contains considerable yellow-green fluid. Intestines empty. From about 2 inches below the pylorus to a point corresponding to the tail of the pancreas, the mucosa is raised in hemorrhagic patches, looking like ulcers (covered with mucus). Spleen not congested, but contains several bullous patches. Kidney and liver show small amount of fatty degeneration. Left adrenal at its larger end markedly hemorrhagic. Pancreas seems slightly congested, showing slight pinkish tinge in contrast to dead white color of fasting pancreas.

*Experiment 36, March 9, 1910: Good Flow; Right Adrenal Removed; Worms and Blood in Intestines*

		Blood-pressure.
9:30 a. m.		180
9:52 a. m.	R. A. O.	116
10:17 a. m.		106
	Juice running freely, no apparent cause for the fall in blood-pressure.	
1:30 p. m.	first cannula full	114
2:41 p. m.	second cannula overfull	clot
	10 min. later	92
3:25 p. m.	third cannula full	72
4:01 p. m.	fourth cannula full	72
4:32 p. m.	fifth cannula full	60
4:58 p. m.	sixth cannula full	clot
5:25 p. m.	seventh cannula full (100)	42
5:45 p. m.	eighth cannula full	38
6:00 p. m.	ninth cannula full	34
6:14 p. m.	tenth cannula full	30
6:26 p. m.	eleventh cannula full	28
6:36:30 p. m.	twelfth cannula full	24
6:46:45 p. m.	thirteenth cannula full	20
6:56:30 p. m.	fourteenth cannula full	clot
7:06 p. m.	fifteenth cannula full	20
7:12:30 p. m.	sixteenth cannula full	16
7:17 p. m.	seventeenth cannula full	Death.

This dog was very strong constitutionally and lived with blood-pressure very low for several hours—longer in that state than the dogs with both adrenals removed do and almost as long as do the normal.

Small amount of blood-stained fluid in peritoneal cavity. Duct clear. Intestine full of uncinariæ in great numbers, and partially digested blood (this may have increased flow). Mucosa looks somewhat roughened. Liver not congested. In intestines considerable blood-stained fluid and some bile; in lower intestines, much dark grumous blood. Spleen not congested; shows one bullous patch. Stomach distended with gas and contains a considerable amount of mucus and bile. Left adrenal looked normal on section.

Juice flowed fairly freely at the beginning of the experiment.

## GROUP 6.—ABDOMINAL INJURY

*Experiment 37, April 4, 1910: Abdomen Injured; Adrenals Intact; Chyme in Intestines*

		Blood-pressure.
9:05 a. m.	Ether	
	Abdomen disturbed for control. Adrenals bluntly dissected, but left intact	142
	Dog quite susceptible to ether	
10:27 a. m.	first cannula full	148
	Juice flowing freely when cannula put in place at onset.	
10:56 a. m.	second cannula full	130
11:28 a. m.	third cannula full	148
12:00 m.	fourth cannula full	156
12:33 p. m.	fifth cannula full	142



		Blood-pressure.
1:00 p. m.	sixth cannula full	138
1:26 p. m.	seventh cannula full	136
1:49 p. m.	eighth cannula full	136
2:15 p. m.	ninth cannula overfull	142
2:31 p. m.	tenth cannula full	142
2:48 p. m.	eleventh cannula full	104
3:12 p. m.	twelfth cannula full	clot
3:29 p. m.	thirteenth cannula full	115
3:46 p. m.	fourteenth cannula overfull	80 *
4:00 p. m.	fifteenth cannula overfull	70 *
4:12 p. m.	sixteenth cannula overfull	54 *
4:22 p. m.	seventeenth cannula full	54 *
4:32 p. m.	eighteenth cannula full	46*
4:41 p. m.	nineteenth cannula full	44*
4:49 p. m.	twentieth cannula full	42
4:57 p. m.	twenty-first cannula full	74
5:06 p. m.	twenty-second cannula full †	72
5:12 p. m.	twenty-third cannula full	52
5:18:30 p. m.	twenty-fourth cannula full	50
	7 min. 30 sec. later twenty-fifth cannula full	40
	5 min. later twenty-sixth cannula full	26
	1 min. 30 sec. later 10 divisions	Death.

\* Blood-pressure-recording pen probably slipped down.

† 105.

Intestines contained chyme within a few inches of pylorus. It will be noticed that a flow existed in this dog from the start. Spleen mottled with dark blue areas. Liver not congested, yellowish. Intestines not congested. Stomach empty. Adrenals both congested and hemorrhages at junction of cortex and medulla.

*Experiment 38, April 6, 1910: Abdominal Injury; Adrenals Bluntly Dissected;  
No Flow*

		Blood-pressure.
9:32 a. m.	Ether	
9:50 a. m.		dissection finished 134
12:09 p. m.		no cannula filled 108
5:07 p. m.		no cannula filled 110
7:02 p. m.	Death	no cannula filled 34

Duct clear. Pancreas and intestines pale rather than congested. Juice moved 11 divisions all day. Spleen contracted, hard, with a few dark blue patches. Liver not congested. Adrenals hemorrhagic between cortex and medulla. Stomach and intestines empty, save for bile. Heart and lungs normal, save that heart is somewhat flaccid.

GROUP 7.—RECORDS OF THE TESTS OF THE VARIOUS SECRETIN PREPARATIONS  
AGAINST EACH OTHER

*Experiment 39: Normal Secretin Versus Terminal Normal Secretin*

Dec. 30, 1909: T. N. S. made from experiment of Dec. 29, 1909 (See Experiment 1).

	N. S.*	caused the filling of 4 cannulas and 45 divisions.†
T. N. S.	" " " " 1	" " 28 "
N. S.	" " " " 4	" " 32 "
T. N. S.	" " " " 1	" " "

N. S. caused the filling of 4 cannulas and 39 divisions.*						
T. N. S.	"	"	"	"	1	"
N. S.	"	"	"	"	3	"

T. N. S. much weaker than N. S.

\* Where the quantity of secretin injected is not specified, inadvertently no record was taken of the amount at the time of the experiment, but it was always either 5 or 10 c.c., and was constant for any given comparison.

† It will be remembered that the cannulas used were marked off into 90 divisions each.

*Experiment 40: Normal Secretin Versus Terminal Normal Secretin*

Jan. 4, 1910: T. N. S. made from experiment of Jan. 3, 1910 (See Experiment 2).

5 c.c.	N. S.	caused the filling of 1 cannula and 38 divisions.
5 c.c.	T. N. S.	" " " " 0 " " 45 "
10 c.c.	N. S.	" " " " 2 " " 44 "

Dog died.

N. S. stronger than T. N. S.

*Experiment 41: Normal Secretin Versus Terminal Normal Secretin*

Jan. 5, 1910: T. N. S. made from experiment of Jan. 3, 1910 (See Experiment 2): repetition of tests of Jan. 4, 1910.

N. S. Cannula stuck.

T. N. S. Accident to apparatus.

10 c.c.	N. S.	caused the filling of 3 cannulas.
10 c.c.	T. N. S.	" " " " 1 " and 69 divisions.
10 c.c.	N. S.	" " " " 2 " " 44 "
10 c.c.	T. N. S.	" " " " 1 " " 48 "

N. S. stronger than T. N. S.

*Experiment 42: Normal Secretin Versus Terminal Adrenal Secretin*

Jan. 7, 1910: T. A. S. made from experiment of Jan. 6, 1910 (See Experiment 10).

7 c.c.	N. S.	caused the filling of 2 cannulas and 48 divisions.
5 c.c.	T. A. S.	" " " " 3 " " 79 "
5 c.c.	N. S.	" " " " 0 " " 72 "
5 c.c.	T. A. S.	" " " " 1 " " 83 "

T. A. S. stronger than N. S.

*Experiment 43: Normal Secretin Versus Terminal Adrenal Secretin*

Feb. 9, 1910: T. A. S. made from experiment of Feb. 8, 1910 (See Experiment 15).

5 c.c.	N. S.	caused the filling of 12 cannulas and 30 divisions.
5 c.c.	T. A. S.	" " " " 10 " " 78 "
5 c.c.	N. S.	" " " " 6 " " 65 "
5 c.c.	T. A. S.	" " " " 4 " " 40 "
5 c.c.	N. S.	" " " " 4 " " 70 "

N. S. stronger than T. A. S.

There was hemorrhage from the dog which gave T. A. S. This may have modified the activity.

*Experiment 44: Normal Secretin Versus Terminal Adrenal Secretin*

Jan. 12, 1910: T. A. S. made from experiment of Jan. 11, 1910 (See Experiment 12).

N. S. caused the filling of 3 cannulas and 25 divisions.

T. A. S.	"	"	"	"	6			
N. S.	"	"	"	"	4	"	"	57 "
T. A. S.	"	"	"	"	5	"	"	37 "
N. S.	"	"	"	"	3	"	"	59 "
T. A. S.	"	"	"	"	5	"	"	83 "
N. S.	"	"	"	"	2	"	"	49 "

T. A. S. more active than N. S.

*Experiment 45: Normal Secretin Versus Terminal Adrenal Secretin*

Feb. 13, 1910: T. A. S. made from experiment of Feb. 12, 1910 (See Experiment 16).

5 c.c. N. S. caused the filling of 6 cannulas and 73 divisions.

5 c.c. T. A. S.	"	"	"	"	3	"	"	32 "
5 c.c. N. S.	"	"	"	"	3	"	"	54 "
5 c.c. T. A. S.	"	"	"	"	3	"	"	41 "
5 c.c. N. S.	"	"	"	"	2	"	"	40 "
5 c.c. T. A. S.	"	"	"	"	2	"	"	82 "
5 c.c. N. S.	"	"	"	"	2	"	"	52 "
5 c.c. T. A. S.	"	"	"	"	4	"	"	59 "
5 c.c. N. S.	"	"	"	"	1	"	"	62 "
5 c.c. T. A. S.	"	"	"	"	2	"	"	30 "

N. S. grows weaker; T. A. S. grows stronger.

Action eventually reversed.

*Experiment 46: Normal Secretin Versus Terminal Adrenal Secretin*

Feb. 14, 1910: T. A. S. made from experiment of Feb. 12, 1910 (See Experiment 16).

N. S. caused the filling of 1 cannula. (Clot.)

T. A. S.	"	"	"	"	3	"	"	and 70 divisions.
N. S.	"	"	"	"	1	"	"	75 "
T. A. S.	"	"	"	"	2	"	"	36 "
N. S.	"	"	"	"	1	"	"	79 "
T. A. S.	"	"	"	"	3	"	"	
N. S.	"	"	"	"	3	"	"	59 "
T. A. S.	"	"	"	"	2	"	"	48 "

T. A. S. stronger than N. S. in all but last pair of tests.

*Experiment 47: Normal Secretin Versus Terminal Adrenal Secretin*

Feb. 18, 1910: T. A. S. made from experiment of Feb. 17, 1910 (See Experiment 17).

5 c.c. N. S. caused the filling of 8 cannulas and 60 divisions.

5 c.c. T. A. S.	"	"	"	"	7	"	"	62 "
5 c.c. N. S.	"	"	"	"	8	"	"	68 "
5 c.c. T. A. S.	"	"	"	"	3	"	"	56 "
5 c.c. N. S.	"	"	"	"	6	"	"	74 "
5 c.c. T. A. S.	"	"	"	"	1	"	"	75 "

N. S. stronger than T. A. S. There was hemorrhage from the dog, which gave the T. A. S. This may have modified the activity. Compare with Experiment 43.

*Experiment 48: Normal Secretin Versus Terminal Normal Secretin*

Feb. 26, 1910: T. N. S. made Feb. 25, 1910, from experiment of Feb. 24, 1910 (See Experiment 4).

5 e.e.	N. S.	caused the filling of 1 cannula and 40 divisions.							
5 e.e.	T. N. S.	" " " " 0 " " 49 "							
5 e.e.	N. S.	" " " " 1 " " 49 "							
5 e.e.	T. N. S.	" " " " 0 " " 20 "							
10 e.e.	N. S.	" " " " 3 " " 31 "							
10 e.e.	T. N. S.	" " " " 1 " " 45 "							

N. S. stronger than T. N. S.

*Experiment 49: Normal Secretin Versus Terminal Normal Secretin*

Jan. 27, 1910: T. N. S. made from experiment of Jan. 13, 1910 (See Experiment 3).

	N. S.	caused the filling of 4 1/5 cannulas.							
T. N. S.	" " " " 2 "								
N. S.	" " " " 5 1/3 "								
T. N. S.	" " " " 1 1/5 "								
N. S.	" " " " 5 1/6 "								
T. N. S.	" " " " 1 + "								

N. S. shows decidedly greater activity than T. N. S.

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## A CASE OF FATAL SODIUM CHLORID POISONING

WITH A BRIEF STUDY OF THE EFFECTS OF THE EXCESSIVE ADMINISTRATION OF SALT ON THE TISSUES\*

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NEW YORK

All are more or less familiar with the effects which follow the excessive administration of sodium chlorid, especially with those of such minor grades as arise, for example, after the ingestion of meats or other foods highly salted or after drinking of water rich in sodium chlorid. Indeed, it is highly probable that the early death said to occur when, other water lacking, sea-water is taken as a beverage, is due for the most part to the direct action of the salt and its effect on the tissues of the body. When through choice or necessity, salt foods are taken in excess and when, at the same time, one is unable to secure the requisite amount of water which Nature demands in this condition, symptoms arise illustrative of the effects of excessive amounts of sodium chlorid. This is a fact well appreciated by frontiersmen, explorers, soldiers, by the primitive races and even by lower animals to a certain degree. The cure of these conditions, when Nature is allowed her way, is automatically brought about by the taking of water until the oversaturation of the tissues and body fluids is reduced to, or near, normal.

In death from thirst, especially when associated with a high external temperature, which favors the rapid evaporation of the liquids of the body through the excretory tracts, it is also highly probable that the end is in part brought about as a result of the concentration of the salts, largely sodium chlorid, in the blood and tissues.

Instances of serious results following the injection of concentrated solutions locally are not so very infrequent and, within my knowledge, it has several times happened that, in the haste and excitement of emergency surgery, too strong a saline solution was mistakenly used instead of one of normal strength. The effects in these cases have commonly been local death of tissue, sometimes with extensive sloughing or subsequent abscess formation, but usually entirely without general symptoms.

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\* Presented at the meeting of the Association of American Physicians, May 5, 1910.

It is also quite possible that some of the deaths which follow saline venous infusion may have accidentally occurred in this manner. This is rather unlikely to be detected in these instances since ordinarily the preexisting symptoms and conditions are of so severe a grade as to render death not unexpected, and therefore a searching inquiry might not be instituted.

Much experimental work has been done as to the effects of concentrated saline on the body, chiefly along physiological and pharmacological lines. In some instances these experiments have been conducted with sodium chlorid, but in most, the heavy salts, notably those of magnesium or the other saline cathartics, have been employed. It is practically certain that most of these substances, when similarly introduced, act very largely as does sodium chlorid, and the changes effected in the tissues experimentally are very similar.

It has been almost universally accepted that most of the salines poison or act through alterations in the intracorpuseular osmotic processes. Of late, work along these lines by improved methods, notably the researches of Meltzer and his school, have demonstrated that, in addition to this well-established reaction, there is a definite individual toxic effect, depending on and varying with the metallic ion employed in each instance. In regard to the toxic action of sodium chlorid, however, most observers state that the action is purely and entirely one of osmotic disturbance, a fact which Joseph and Meltzer<sup>1</sup> also admit has not been disproved by their experiments, designed to elucidate this point, although these authors, nevertheless, apparently mean to suggest their personal belief somewhat to the contrary. As a result of this last-mentioned research, it has been shown that sodium chlorid is the least toxic of the group of similar metal chlorids, possibly partly owing to its lesser molecular weight. For dogs, Joseph and Meltzer established a dose of 63 c.c. of sodium chlorid per kilo of body weight, but as those authors patently suggest, this applies to dogs only and the experiments of Loeb, for example, have shown a greater degree of toxicity toward the eggs of *Fundulus*.

So far as I have been able to ascertain, the following case of human poisoning by common salt is entirely unique in medical literature, notably in the fact that the drug was introduced in this case through the intestine and that it produced speedy death. I have therefore considered the instance important enough to report, together with a very brief study designed to verify the conclusions as to the cause of death and to demon-

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1. Joseph and Meltzer: *Jour. Pharmacol. and Exper. Therap.*, 1909, i, 1.

strate, so far as possible, the manner in which this end was probably brought about.

The case was personally reported to me by Dr. W. T. Bivings, of Atlanta, Ga.

#### REPORT AND DISCUSSION OF CASE

A vigorous young woman weighing about 124 pounds was operated on during the quiescent period for chronic appendicitis. The operation was in every way successful and the patient left the table in twenty minutes. After forty minutes she had fully recovered from the anesthetic. Postoperative pulse, respiration and temperature were practically normal.

A rectal enema composed of one pint physiologic saline and half an ounce of whiskey was ordered to be repeated every hour for three doses.

One hour after the first enema, the patient became quite restless and nervous and complained of thirst. At the second dose these symptoms became more exaggerated and she begged continuously for the bed-pan. The condition was then reported to the surgeon. A third enema, however, was given before his arrival, when he found the patient unconscious, with small pulse, 120, and a temperature of 101 F. The pupils were contracted and failed to react to light. The conjunctivæ were injected and tears poured copiously from the eyes.

The temperature rapidly rose to 109 F. (rectal), the respirations became very rapid, shallow and difficult, the pulse quick and small. The patient died about eight hours after leaving the table. Forty minutes before death she had a convulsive seizure lasting ten minutes. A few minutes before death about one quart of blood-stained, gelatinous material was discharged from the intestine. Respiration ceased five minutes before the radial and cardiac pulsations. No autopsy could be obtained.

The urine, which had been frequently voided during the attack, showed an average specific gravity of 1.015. No sugar was present, and no albumin.

Several days afterward, it was discovered that the nurse, who had been appointed to the case by the family, had given, instead of normal saline, an enema of nearly saturated sodium chlorid, provided and labeled in the operating-room as a "stock solution." The patient had thus received nearly 9 ounces of sodium chlorid.

After fully considering the case with a study of the physiological effects of concentrated saline solutions on the organism, and other possibilities apparently having been eliminated, it was concluded that death was caused by the concentrated saline, the action of which was probably accentuated by the natural reduction of body resistance consequent on the operation.

Certain of the conditions manifested by this patient particularly substantiate this assumption. The rapid and high elevation of temperature is characteristic of those disease conditions in which the fluids of the body are rapidly reduced, as, for example, in acute dysentery and in cholera. The active lacrimation and the diuresis are also cardinal symptoms in the picture following oversaturation of the body fluids with salt,

acting according to some by stimulation of the glandular cells, as by caffein, but perhaps, as Cushny states, chiefly by the elevation of the capillary pressure.

The convulsive attacks were doubtless caused by the withdrawal of fluid from the central nervous tissues as a whole and particularly by the direct effects of this abnormal osmosis on the ganglion cells. The succeeding comatose state is similarly explained, though perhaps partly also by the "curare-like action" of sodium chlorid on the motor nerve endings, as suggested by Joseph and Meltzer. I believe that special corroborative stress may also be laid on the fact that respiration ceased in this patient before the heart action, a sign observed in all instances of sodium chlorid poisoning by Joseph and Meltzer.

In order that the probable relationship between the administration of the concentrated saline and the symptoms in this case might be further shown, and the precise way in which the chemical affected the tissues demonstrated, the following experiments were conducted at the Montefiore laboratory by Dr. D. M. Kaplan and myself.

#### REPORT AND DISCUSSION OF EXPERIMENTS

Rabbits were chosen for the experimentation both on account of the facility with which they might be handled and, also, because this animal, which rarely or never regurgitates, appears therefore to be most available for tube-feeding. Preliminary experiments on dogs, cats and rabbits soon demonstrated that direct imitation of the conditions pertaining in the case were not practical, as the colon rapidly ejected the concentrated solution. The saline was therefore introduced by the stomach-tube.

EXPERIMENT 1.—"Young rabbit weighing 2 pounds and 14 ounces selected. Ten grams of sodium chlorid, dissolved in 25 c.c. of water, are introduced by the tube into the stomach of the fasting rabbit. Five minutes later the animal voids 33 c.c. of clear, albumin-free urine. The animal is restless, the breathing shallow, the ears pale. It falls down in a semiconvulsive attack, but regains station to sink again on haunches. It appears as though suffering from colic, rises, then falls; after fifteen minutes, voids 15 c.c. of urine, which subsequent examination demonstrates to be natural, except for a very high chlorid content. One hour after the dose the animal still shows symptoms of restlessness and abdominal pain and at times of convulsive seizures; passes 9 c.c. of urine similar to previous specimen, except that the content of sodium chlorid was found to be still greater. The animal becomes unconscious, the comatose condition being interrupted from time to time by a constant fine muscular tremor and by convulsive seizures. The respiration becomes shallow and very much slowed. The ears are very pale and the peripheral circulation very slight. The heart-sounds still remain regular, but very rapid and weak." One hour and seven minutes after the sodium chlorid had been given the animal died in a convulsion of slight severity. Fifty-seven c.c. of urine in all was passed between



the time of dosage and that of death. The specimens examined quantitatively showed a progressive increase of sodium chlorid, but no other evidences of disease.

*Autopsy.*—The post-mortem examination shows that the peritoneal cavity contains a considerable quantity of semigelatinous lymph. The entire intestine is distended with a thick gelatinous mucoid secretion and numerous minute hemorrhagic extravasations are found in the submucosa. The stomach is similarly filled with gelatinous mucus, slightly blood-stained, and considerable areas of submucous extravasation are present, marked by large areas of clotted blood. The liver tissue is grossly normal. The kidneys are edematous and anemic, but otherwise normal. The heart is relaxed and contains a small amount of dry clotted blood. The muscle walls are apparently edematous. The lungs are notably bloodless, otherwise normal. The skeletal muscles are dry and the blood-vessels throughout filled by a scant dry clot with notably diminished fluid. The encephalon is anemic, tissue being somewhat edematous.

Microscopic examination shows no apparent alteration either in the tubules or in the glomeruli of the kidney. The blood-vessels are moderately filled by apparently unchanged blood-cells and the tissue throughout appears to be normal. The liver shows a marked alteration in the gland-cells, especially in those most adjacent to the sublobular radicles. The change consists in a thinning out of the protoplasmic structure, resulting in a washed-out appearance similar to that seen in very marked edema. All except the finely granular elements of the cell cytoplasm appears to have been washed away. No vascular or interstitial alterations are apparent. The cells of the heart muscle appear in some areas swollen and edematous; in other places the fibers appear shrunken and desiccated, as though hardened rapidly in too intense fixative agent.

In places the mucosa of the stomach shows a complete necrosis of the tubules, as though from the action of some strong escharotic; the hemorrhagic extravasations are present both in the submucosa and in the mucosa and are, of course, associated with extensive acute destruction of the adjacent tissues. The submucosa is infiltrated with an edematous exudate, which has torn apart and separated the fibrils of the submucosa. In some areas, aside from the submucous edema, the structure is apparently normal.

Sections through the cerebrum show an almost universal dilation of the perivascular lymph-spaces with alternating areas of apparent desiccation and edema in the diffuse tissue. Many of the ganglion cells are atrophied, shrunken and chromatophilic, as though from fixation in a too rapid and too strong hardening agent. In a few areas the cells appear to be acutely swollen and almost disintegrated.

EXPERIMENT 2.—A full-sized adult rabbit weighing 4 pounds and 9 ounces was given 20 gm. of sodium chlorid in 40 c.c. of water, introduced into stomach through the tube. "Symptoms appear in fifteen minutes, rapid and shallow breathing with great restlessness being first noticed. After thirty-five minutes, very marked peristalsis can be noted through the abdominal walls, which have meantime become somewhat distended. Urine is passed at frequent intervals, though in small quantities. Comatose attacks alternate with great restlessness, and at times the animal appears to be in pain or much frightened, at other times so somnolent as to be almost anesthetic. Convulsive attacks of slight degree and an almost constant muscular tremor is apparent. The breathing is constantly labored." The animal finally died in a convulsive seizure one hour and forty-five minutes after the dose had been administered. During this time a total of 36 c.c. of highly colored urine was passed. No albumin was present and no blood or casts, but the urine showed a progressive and finally a very marked increase in the chlorids, the last specimens being of very high specific gravity.

*Autopsy.*—The necropsy showed a very early and marked degree of post-mortem rigidity. The abdomen was markedly distended, and the peritoneal cavity contained a considerable amount of gelatinous, slightly blood-stained lymph. The colon was found normal, but the small intestine was distended with gelatinous mucus, not blood-stained, however, and no extravasations were apparent in the walls of the intestine. The stomach was much distended with gas and with blood-stained mucus; this distention was so marked as to cause minute rents to appear in the muscular wall. Large areas of escharotic tissue and of submucous hemorrhage were apparent in the mucosa. The liver showed no gross change, but the kidneys appeared very edematous. The lungs were notably dry, a condition also very marked in the skeletal muscles, but marked edema of the heart muscle and of the encephalon was apparent.

"Microscopic examination shows a very marked edematous swelling of the liver cells, much more marked about the central veins, a few areas of small round-cell infiltration adjoining the interstitium and a notably diminished amount of blood in the venules and capillaries. The kidneys show marked edema with disintegration of the cells of the convoluted tubes in particular. The outlines of the cells are indistinct, the cytoplasm very granular and edematous in appearance and many of the tubules are nearly filled by a granular cell detritus. No changes are apparent in the glomeruli, and nothing abnormal can be recognized in the blood vessels. The heart-cells show shrinkage of the fibers in places and edematous swelling in others. The lymph-spaces are apparently much dilated. There is an almost complete necrosis of the upper layers of the gastric mucosa: there are extensive patches in which the ischemia extends down to the basement membrane. The hemorrhagic extravasations extend from the submucosa to the upper surfaces of the mucosa in the most extensively involved areas. There is a general edema of the submucosa throughout. There is a diffuse edema apparent in the tissues of the cerebrum. Most of the ganglion cells show swelling and there is a general chromatolysis. Occasional cells show an increased coloration, selecting a diffuse nuclear dye, together with a shrinkage of the cells. The perivascular lymph-spaces are quite universally distended."

The symptoms produced in these two experiments are quite similar to those manifested by the case under study. The lesions found are apparently the result of the abnormal saturation of the tissues with salt and a resulting visceral edema following the abstraction of excessive quantities of fluid from the circulating media. The blood was scanty throughout, due evidently to abstraction of its fluids to satisfy the hypersaline tonicity of the tissues, none the less, in even favorable sections, pronounced red-cell deformity or excessive crenation of the red cells was not seen, indicating, apparently, that as yet the salt content of the blood did not balance that of the tissues, a condition quite in accord with previous experiments in which saline had been introduced into the intestinal canal.

Although the proportion of salt given to body weight was probably proportionately greater in the animals than in the case reported, I think but little doubt can be entertained but that lesions akin to those in the experimental animals were present and that death was induced as a result of them.

I was personally much impressed with the fact that no inflammatory changes developed in the kidneys as a result of the excretion of so concentrated a fluid, for careful chemical examinations of the urine by Dr. Kaplan showed a constantly increasing excretion of sodium chlorid. This certainly indicates in the animals, as also in the patient, that death was not due to inadequate capacity on the part of the kidneys to excrete the excessive salt, but points rather to the insufficiency of the liquid present in the body to satisfy the salt while still maintaining the blood in a normally fluid state for the maintenance of the vital tissues in a physiological condition.

Certain apparent discrepancies exist in the varying tissues studied in the two experimental animals. Thus, in each, some viscera were found edematous, others even abnormally dry, and in the two practically similar experiments the lesions were not comparably constant. This I believe to be satisfactorily explained by the fact that death occurred soon after the administration of the salt and before the osmotic pressures had time to become balanced; until this has taken place, according to Cushny, a continuous variation in the osmotic flow must occur.

In order that some idea might be gained as to the action of protracted excessive doses of sodium chlorid, especially on the kidneys, the following experiment was made:

EXPERIMENT 3.—An adult rabbit weighing 4 pounds and 4 ounces was selected. Two grams of sodium chlorid in 10 c.c. of water was administered on alternate days for thirteen times. After a rest of seven days, 5 gm. in 20 c.c. of water was given and similarly five days later 6 gm. Twelve days later 7 gm. was administered and, again, after two days 7 gm. Soon after this the animal died, giving an acute symptom-picture similar, except in a much milder degree, to that seen in the acute experiments. In all, 72 gm. of sodium chlorid were thus given in a space of eighty-five days. The saline was given in each instance dissolved in a sufficient bulk of water, the idea being to avoid the local escharotic action of the concentrated saline on the gastric mucosa. The initial and each succeeding increased dose was followed by the appearance of symptoms like those manifested in the acute poisoning, but of much less intense degree and of lesser duration. When the doses were given on alternate days, the symptoms became progressively less marked as the dose was continued. The animal showed, from the first, very rapid emaciation, although it was abundantly fed throughout. Frequent examinations of the urine showed the rapid excretion of the chlorid without the appearance of sugar, albumin or other evidence of renal disease.

*Autopsy.*—This showed no gross changes except for the presence of a gelatinous exudate in the intestine. No scarred areas were demonstrable in the gastric mucosa and no gross lesions of the other viscera, except for the edematous appearance of the brain, liver and heart. The skeletal muscles showed a strikingly dry appearance.

Microscopic examination of the kidney shows swelling and granular alteration in the cells of the collecting tubes, but there is no change apparent in

the interstitial tissue or in the glomeruli. The blood-vessels, notably the larger capillaries, are distended with blood and in places minute extravasations have taken place. The lesions are therefore apparently entirely of an acute type.

The liver shows very little change. Some of the cells appear swollen and slightly edematous; a few are somewhat disintegrated and the interstitial tissue seems to show in places a more than normal infiltration with lymphocytes. The blood-vessels are naturally filled with blood, and no other change is obvious.

No changes can be made out in the heart-muscle. The lung is normal except for occasional areas of edema. The stomach shows occasional small areas of necrosis affecting the superficial portions of the mucosa only.

The brain shows in places a marked accumulation of small round cells about the smaller arterioles. There is an almost universal dilatation of the perivascular lymph-spaces, but no changes can be made out in the ganglion cells.

This last experiment was repeated with practically identical results, beginning with 1 gm. of salt daily, finally terminating with 7 gm. of concentrated saline, which caused death, whereas 7 gm. previously given in greater dilution failed to cause other than temporary disturbance.

#### CONCLUSIONS

The symptoms occurring in Dr. Bivings' case have been reproduced substantially in the poisoning of rabbits by concentrated saline. From the lesions, as well as from the symptoms which developed in both the woman and the animals, it seems certain that the symptoms were largely or entirely due to the concentration of the saline rather than entirely from the amount of salt actually taken into the body. Even in these extreme examples the excretion of the excess salt was rapidly brought about and that without producing either symptoms or lesions of a very grave nature in so far as the kidneys were concerned.

From this brief study there seems to be no doubt but that the deleterious action of the salt lies in the fact that fluid is rapidly abstracted from the blood both for excretion and in effecting local edema, especially of the larger solid viscera. This is followed by a consequent concentration of the blood, the most serious results of which appear to follow from the lessened supply to the ganglion cells.

In so far as this study goes, the older theory that sodium chlorid acts only by osmotic disturbance seems to be substantiated.

A broad question opened up by this well-recognized action of the concentrated salines is that of the importance of the fluidity of the blood in many disease conditions, especially such as in some forms of typhoid or dysentery, in which the frequent intestinal discharges so diminish the fluid of the blood as to cause symptoms of a somewhat similar nature to develop.

Most of us have observed from time to time similar symptoms in patients after the saline cathartics, especially those in concentrated form, have been persistently given, and it seems very wise to bear this action in mind in the management of cases in which concentration of the body fluids may occur.

The failure of the sodium chlorid, used medicinally or dietetically, to produce renal changes other than such as evidently occur only as a result of local edema and disturbed osmosis, would apparently indicate that, in all probability, the bad results which the chlorids produce in certain types of nephritis are due not so much to an irritant or toxic action of the salt on the kidney tissue, as its effect on the fluidity of the blood and on osmosis.

44 West Ninth Street.

## AN EXPERIMENTAL STUDY OF THE RESISTANCE TO COMPRESSION OF THE ARTERIAL WALL \*

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NEW YORK

The object of this study was to determine whether the resistance to compression of the arterial wall introduces an error of any importance in the clinical measurement of systolic blood-pressure by methods employing circular compression of the arm.

### PREVIOUS STUDIES AND PRESENT STATUS OF THE QUESTION

Very few studies of this problem have been made, and none of these can stand criticism. Von Basch<sup>1</sup> measured crudely the pressure necessary to close the empty radial artery. He found that this was 1 mm. for normal, and not much above 5 mm. for sclerotic vessels.

Martin,<sup>2</sup> in a few experiments on the normal carotids of man, horse, and dog, found that a pressure of 2 mm. was sufficient to collapse the arterial wall; in arteries from an advanced case of arteriosclerosis only 7 mm. were required.

No subsequent direct experiments were made, until those in 1908, by Herringham and Womack,<sup>3</sup> who examined carotid, iliac and brachial arteries removed post mortem from forty-nine bodies. The results were very startling, showing wide variations in the compressibility of these vessels, the extremes in the case of the brachials being from 4 to 34 mm. These variations could not be brought into relation with the age of the individual the condition of the arterial wall, its expansibility under high internal pressure, or the disease causing death. Furthermore, marked differences were found between carotid, iliac and brachial from the same individual, and the two brachials differed by as much as 10 mm.

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\* From the Department of Practice of Medicine and the Maria McLean Proudfit Fellowship in Medicine, in the College of Physicians and Surgeons, Columbia University, New York.

1. Von Basch, S.: *Der Sphygmomanometer und seine Verwerthung in der Praxis*, Berl. klin. Wchnschr., 1887, xxiv, 181.

2. Martin, C. J.: *The Determination of Arterial Blood-Pressure in Clinical Practice*, Brit. Med. Jour., 1905, i, 865.

3. Herringham, W. P., and Womack, F.: *Proc. Roy. Soc. Med.*, 1908, ii, 37. (Med. Sect.)

The obvious criticism of these results, as casting a doubt on human blood-pressure measurements, is that they were obtained from work on dead arteries; this criticism was promptly made by Hill,<sup>4</sup> who also objected that, for proper comparison, blockage of the pulse-wave and not cessation of the flow should be the criterion. Herringham<sup>5</sup> subsequently, in a discussion of the subject, cited a few further experiments performed on arteries killed by soaking in sodium fluorid solution and still showing an appreciable resistance to compression, the highest being 22 mm.; and an especially high figure was obtained from a patient who had had hypertension during life. He considered that these experiments were a sufficient reply to Hill's objection.

Since the completion of our work, two new papers have appeared, reporting observations of a different kind. Scholtyssek<sup>6</sup> performed a few experiments similar to Herringham and Womack's, using arteries from the dog, rabbit, and horse, and two human vessels. In all cases the arteries were compressed at less than 3 mm. Hg, except one digital artery from the horse, which required 24 mm. The circulating medium seems to have been water; temperature was disregarded, and a very low internal pressure appears to have been used. Scholtyssek also tested the resistance of a living carotid from a rabbit. Attaching it to one carotid of another animal, thus maintaining in it a normal blood circulation, the pressure necessary to obliterate the flow from it was determined, while direct manometric readings were made from the opposite carotid. His results he considered showed a resistance of 2 mm. Hg for the rabbit's carotid; of 7, 8, 15, and 11 mm. Hg for a dog's, similarly tested. The most obvious criticism of these figures is that there was not absolute synchronism between his readings of compressibility and the rapidly fluctuating blood-pressure of the animal, since the former were not recorded graphically. The results, however, have real relative value, though the vessels of such small animals are scarcely comparable with the human brachial.

Schmidt<sup>7</sup> describes a number of observations on freshly removed dog and rabbit arteries by a similar method. He tested, in rather unsystematic fashion, the effect of varying internal pressure, of temperature, of painting with epinephrin and with chloral hydrate and of death of the vessels. Physiologic saline solution or blood were his circulating media.

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4. Hill, L.: The Measurement of Systolic Blood-Pressure in Man. *Heart*, 1909, i, 73.

5. Herringham, W. P.: *Proc. Roy. Soc. Med.*, 1909, ii, 238. (Med. Sect.)

6. Scholtyssek, August: *Arch. f. Anat. u. Physiol.*, 1909, *Physiol. Abt.*, p. 323.

7. Schmidt, Magnus: *Arch. f. Anat. u. Physiol.*, 1909, *Physiol. Abt.*, p. 331.

He concludes that the resistance varies with the vessel and with the time after removal, no more change in resistance occurring after twenty-four hours. With increase of the internal pressure, the resistance may increase, diminish, or remain constant. With large arteries from these animals he found the resistance to range between 1.84 and 1.38 mm. Hg. He was unable to produce noticeable constriction by painting with epinephrin, or dilatation by chloral hydrate. He did obtain changes associated with temperature; the higher the temperature the lower the resistance to compression.

This work is open to many of the objections urged against the preceding. In addition, it may be objected that segments of artery only 3.5 to 4 cm. long were used. This is of less importance than with thicker vessels, though not negligible. Schmidt evidently dealt with live arteries, and his work is of interest on that account, but the conditions were not accurately controlled. As with Scholtyssek's experiments, the results do little to solve the problem of the resistance to compression of the human brachial artery.

Others have either approached the problem by altogether indirect methods, or, accepting von Basch's figures, have considered the arterial wall a negligible factor in clinical blood-pressure measurement. To the latter opinion, one of us<sup>8</sup> has formerly held.

Williamson<sup>9</sup> has made a study of the question by comparison of the systolic pressures in the arm and leg. He claims to have found very marked differences in high-pressure cases, which he interprets as due altogether to the vessel-wall factor, assuming that the thickness of the wall of the leg arteries and extensive arteriosclerosis in them is quite regularly greater than in the brachial artery.

Hill, in his discussion of the paper and his subsequent publication,<sup>4</sup> takes direct issue with Williamson on the accuracy of his observations and has shown how slight tension in the leg muscles, or lack of simultaneous measurement of the pressure, may lead to serious error in the result. Hill's own investigation of the blood-pressure in the arm and leg failed to show any appreciable difference in the readings, if certain precautions were taken, except in the case of free aortic regurgitation. Hill has also shown that the superficial venous pressure may be raised to within 10 mm. of the obliterating pressure in the brachial, as measured by the armlet, and has made measurements from two arteries at different levels, which differed by exactly the hydrostatic pressure of the blood-

8. Janeway, T. C.: *The Clinical Study of Blood-Pressure*, D. Appleton & Co., New York and London, 1904, p. 60.

9. Williamson: *Proc. Roy. Soc. Med.*, 1909, ii. (Med. Sect.), 229.



column which separated them. Hill concludes that we have no evidence that the resistance of the arterial wall to compression affects the systolic index of blood-pressure, but that the relative softness or hardness of the arterial wall affects the conduction of the systolic wave and so modifies the readings. These readings, however, would in his opinion correspond to real differences in the systolic pressure within the arteries.

Oliver,<sup>10</sup> also approaching the question by an indirect method, namely, comparison of the measurement by an armlet with the measurement by his hemodynamometer, considers that he has demonstrated very large errors in the systolic pressure measured by the armlet method: that human arterial pressure, even in disease, seldom exceeds 200 mm. and never rises above 250 mm., all higher readings being due to factors inherent in the vessel-wall.

Von Recklinghausen<sup>11</sup> has shown how sclerotic vessels may be obliterated at the center, but stand open at the corners, as an explanation of the mechanical difficulties in the way of easy compression of thick-walled vessels.

On the other hand, such observations as that of Hensen,<sup>12</sup> of extremely low systolic readings in a sclerotic brachial artery, and similar ones which all who use the sphygmomanometer extensively have encountered, have seemed to make any marked influence of the sclerotic vessel-wall very questionable.

Finally, Russell,<sup>13</sup> in his recent book, takes the ground, altogether from *a priori* considerations, that the state of tonus of the vessel-wall is probably even more important than the actual blood-pressure in producing the high readings obtained by our clinical instruments. Hypertonus of the vessel-wall, rather than arterial hypertension, is what he believes is measured. Russell adduces no experimental evidence, except from an artificial scheme with rubber tubing, but takes the stand that such high blood-pressure readings as are clinically recorded are inconceivable; that most of the variations in these readings, occurring spontaneously or produced by drugs, are due to change in the tonus of the vessel examined; and, though conceding the value of the sphygmomanometer for measuring these variations in vessel tonus, insists that the estimation of the caliber

10. Oliver, G.: *Studies in Blood-Pressure*, Ed. 2. H. K. Lewis, London, 1908, p. 111.

11. V. Recklinghausen, H.: *Ueber Blutdruckmessung beim Menschen*. Arch. f. exper. Path. u. Pharmacol., 1901, xlii, 78.

12. Hensen, H.: *Beitrag zur Physiologie und Pathologie des Blutdrucks*. Deutsch. Arch. f. klin. Med., 1900, lxvii, 443.

13. Russell, W.: *Arterial Hypertonus, Sclerosis and Blood-Pressure*. J. B. Lippincott Co., Philadelphia, 1908, p. 87.

and degree of contraction of the radial artery by the educated finger is still more important. Russell does not explain clearly how such extreme hypertonic contraction of the vessels can fail to be associated with marked increase in the peripheral resistance and therefore of the blood-pressure. One gains the impression from his book that extreme hypertonus of such large arteries as the brachial or radial occurs independently of constriction of the arterioles. He also goes so far as to state that rubber tubing is a more accurate counterpart of the living artery than are dead arteries removed post mortem.

The only other work in any way bearing on the problem at issue has been a comparison of the indirect manometric blood-pressure record, made during the course of an amputation, with simultaneous indirect readings made on the other arm or leg. Such observations have been published by Müller and Blauel<sup>14</sup> and more recently by Volhard.<sup>15</sup>

With the von Recklinghausen apparatus and 12 cm. armlet, Müller and Blauel found that it required a pressure of 7 to 10 mm. above the true systolic pressure within the artery to obliterate the pulse-wave. With the Gärtner method, or still more with the old Riva-Rocci apparatus and its narrow armpiece, this error became greatly exaggerated. The patients all had approximately normal vessels. Volhard reports a slightly greater difference, 13 mm., in a patient with normal blood-pressure and as much as 20 mm. in one with hypertension. He only alluded to his results somewhat briefly.

Since one of us<sup>16</sup> has shown that the soft tissues of the arm are practically negligible as a source of error, these results speak strongly for some influence of the artery wall.

These altogether conflicting views, and the disagreement in the results obtained by indirect methods of approaching the problem, pointed so clearly to the need for accurate experimental data obtained under conditions which should be beyond criticism, that we were impelled to undertake the study of the question by methods subsequently described.

#### PLAN OF THE EXPERIMENTS

The plan originally in mind was to study the compressibility of human arteries, adults' and infants', obtained post mortem, with a view to determining the influence of thickness of wall, atheroma and calcification; and

14. Müller and Blauel: Zur Kritik des Riva-Roccischen und Gärtnerschen Sphygmomanometers. *Deutsch. Arch. f. klin. Med.*, 1907, xci, 317.

15. Volhard: Ueber die Messung des diastolischen Blutdrucks beim Menschen, *Verhandl. d. Cong. f. innere Med.*, 1909, xxvi, 200.

16. Janeway, T. C.: The Influence of the Soft Tissues of the Arm on Clinical Blood-Pressure Determinations. *THE ARCHIVES INT. MED.*, 1909, iii, 474.

to attempt to study the compressibility of surviving human arteries obtained from amputated limbs. It was hoped that from these, not only might an accurate idea of the compressibility of live arteries be obtained, but that the influence of tonus might also be tested, by introducing epinephrin into the circulation through the vessel. Such arteries, however, proved very difficult to procure and had many small branches requiring ligature. The experiments were rather unsatisfactory, because of the doubt as to the life of the vessel, when finally prepared; and their number was insufficient to give conclusive result.

Since Meyer<sup>17</sup> has shown that the carotid of the ox, kept in ice-cold Ringer's solution, preserves for days its capacity for responding to electrical stimulation, epinephrin and other vasoconstrictors, ox carotids, brought from the slaughter-house in cold Ringer's solution, were used for the study of the effects of tonus, and later a few experiments were done on mesenteric arteries from the ox.

Meyer<sup>17</sup> found extreme contraction in ox carotids removed in this way, which in his experiments required stretching with heavy loads to overcome; and MacWilliam and Mackie<sup>18</sup> have noted a similar persistence of contraction in certain post-mortem arteries and arteries removed at amputation. It seemed to us, as to them, that herein might lie the chief explanation of Herringham and Womack's<sup>3</sup> discrepant results. Therefore we believed that measurements made on surviving animal arteries, under varying absolutely known conditions, would give information of far more value for the elucidation of the physiological question at issue than the study of many dead arteries.

Finally, the plan included a study of the compressibility at different internal pressures, of the influence of the length of the segment of vessel examined, of other sources of experimental error, and the testing of some elastic and non-elastic tubes other than arteries.

#### MATERIAL EXAMINED

The material examined was as follows:

1. Twelve common carotids from infants, removed post mortem, of which ten gave results free from obvious error.
2. Twenty-three common carotids and four iliaes taken from adults, removed post mortem, of which twenty gave results free from obvious error.

17. Meyer, O. B.: Ueber einige Eigenschaften der Gefäßmuskulatur mit besondere Berücksichtigung der Adrenalinwirkung, *Ztschr. f. Biol.*, 1906, xlviii, 352.

18. MacWilliam, J. A., and Mackie, A. H.: Observations on Arteries, Normal and Pathological, *Brit. Med. Jour.*, 1908, ii, 1477.

3. Six arteries taken from amputated limbs, of which four gave results free from obvious error.

4. Thirty-eight common carotids and four mesenterics from the ox, of which eleven gave results free from obvious experimental error.

5. Six samples of rubber tubing of different caliber and lumen; one boiled artery; one esophagus; one segment of a small intestine.

## METHOD

### I. APPARATUS

The artery *A A* (Fig. 1) to be examined, after careful ligation of its branches a short distance from their emergence, was tied securely over the ends of two glass cannulas *B, B'*. Except in the case of the infants' arteries, these cannulas were cut off squarely; for the smallest infants' vessels beveled cannulas had to be used, but these we believe may be a source of error, a small portion of the artery being collapsed over the opening of the cannula before its lumen elsewhere has

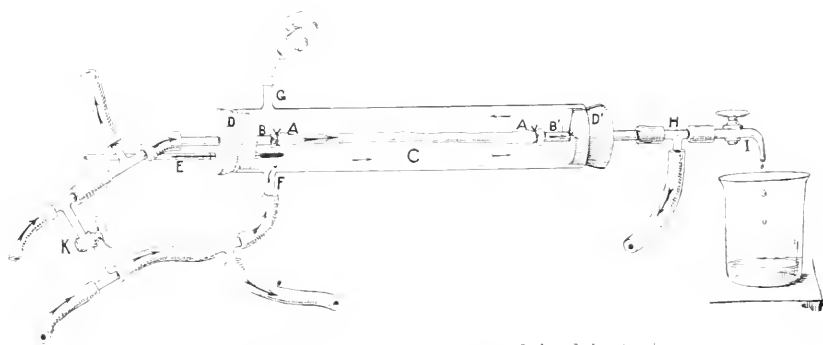


Fig. 1.—Diagram of apparatus explained in text.

been obliterated. The artery was then placed in a glass cylinder *C*, of 21 cm. length and 2.5 cm. diameter, with a capacity of 52.5 c.c. after insertion of the stoppers, as shown in Figure 1. The cannulas, *B, B'*, project through rubber stoppers, *D, D'*, at either end. For convenience in the insertion and removal of the vessel, one of these stoppers, *D'*, was split through one-half its diameter. The other stopper, *D*, was pierced by a second opening for the insertion of the thermomometer, *E*. The cylinder carried near one end two glass tubes, *F, G*, set in opposite points of its circumference and communicating with its lumen. The lower of these tubes, *F*, was connected by rubber tubing with a pressure-bulb, which was suspended from the ceiling by a pulley and rope and could be raised and lowered at will, and which will be called the external circulation, and through a T tube with a recording mercury manometer, which at all times registered the pressure in the external circulation and the cylinder. The upper tube, *G*, was for the escape of air from the cylinder in filling, after which it was closed by a rubber tube and pinch-cock. The cannula, *B*, was similarly connected with a pressure-bulb which could be raised or lowered at will, which will be spoken of as the internal circulation and by a T tube with a recording mercury manometer. The other cannula, *B'*, was connected by rubber tubing with a T tube, *H*, the stem of which was connected by pressure-tubing with a Hürthle membrane manometer.

The opposite end of the T tube was connected by rubber tubing with a capillary tube armed with a stop-cock.

The manometers connected with external and internal circulations, and the Hürthle manometer, which registered the pressure changes in the outflow from the artery, were made to write on a kymograph, and all the steps in the experiment were graphically recorded. For convenience, the manometer attached to the internal circulation was made to write a little distance (about 10 mm.) above that of the external circulation, and just enough behind it, so that the writing points did not touch, when at the same height. The Hürthle manometer record was carried at the bottom of the drum. In order to obviate the complication of two zero lines, where only differences in pressure were to be measured, the two circulations were connected by the branch K, closed by a stop-cock. Before and after each reading, this stop-cock was opened and the pressure in the two circulations allowed to equalize. The relative positions of the two manometers were then recorded. These lines of equal pressure were used for all subsequent measurements, and the approximate actual internal pressure, as measured by a scale on the manometer, was written on the tracing, if this was varied during the course of an experiment.

For the experiments on live arteries, two other pressure-bulbs were employed, connected with the internal circulation just before its attachment to the cannula, B, by means of a Y tube. All the rubber tubing used was the heaviest pressure-tubing of 3 mm. bore. The cylinder containing the artery was itself encased in a large water-jacket, which has been omitted from the diagram for the sake of simplicity. The internal circulations were also carried through large water-jackets in spiral glass tubes. The various water-jackets were connected with one another and a uniform circulation maintained through them, by means of which both the internal and external circulations were always kept at the same temperature, which could be varied between that of tap-water, about 15 C., and 37 C.

#### II. TECHNIC FOR POST-MORTEM ARTERIES

The technic of the measurement of the compressibility in any post-mortem vessel was as follows: The artery was placed in the cylinder with great care to avoid any twisting on its axis or undue longitudinal stretching. The flow was then established through it from the internal circulation, until all the air had been driven out through the capillary and Hürthle manometer. The external circulation was then connected with the cylinder until the latter was filled, and the last bubble of air driven out through the tube G. The circulations were then connected through the branch K, and the manometer heights and the position of the Hürthle manometer recorded. The drum was then stopped and the branch K closed. The bulb of the external circulation was then slowly raised until the lever of the Hürthle manometer began to fall, when the drum was again started, and this pressure, marking the beginning of collapse of the artery, recorded. This corresponded as a rule to a marked diminution in the outflow from the capillary.

The drum was again stopped and the pressure in the external circulation gradually raised until no drops whatever came from the capillary. The Hürthle manometer was then at zero, and another record at this point, the point of complete obliteration of the artery, was made. The stop-cock in the capillary was then closed and the pressure in the external circulation gradually lowered until the lever of the Hürthle manometer began to rise. A record of this point was also made. Frequently a single drop would get through the vessel without the flow being reestablished, apparently owing to a little unevenness in the lowering of the pressure, so that waves were produced. If so, the lowering was continued until the Hürthle manometer showed a visible continued rise. This corresponded to an

outflow from the capillary of about one drop every three seconds. This point was considered the pressure at which flow through the artery was resumed.

After this the bulb was lowered to the original point, the stop-cock on the branch K was reopened, and another reading recorded after the pressures had equalized. In the case of post-mortem vessels, such readings were made with internal pressures of 30 mm., 100 mm. and 150 mm. Hg. In these experiments the temperature was not controlled. Ringer's solution was used for both the internal and external circulation in all the experiments, except in experiments in which it was desired to test the effect of other substances.

### III. TECHNIC FOR SURVIVING ARTERIES

In the experiments on living vessels the technic was somewhat different, and was a matter of great importance. Only after a number of experiments were our results free from the various sources of error described below. The arteries were roughly removed from the animal with the surrounding fascia and fat and put at once in a large jar of ice-cold Ringer's solution, in which they were brought to the laboratory. The artery was then dissected free from its sheath, with as little removal from the solution as possible, and the branches ligatured as found, care being taken that the ligatures were placed a short distance from the origin of a branch, in order to avoid any deformation of the artery itself.

A portion of the artery, not less than 7 cm. long, was then cut off and the cannulas inserted into its ends and securely tied. The vessel and the cannulas were then left in cold Ringer's solution until a segment of the remainder of the vessel 8 mm. long had been cut off. The ring thus obtained was cut across, making a strip, which was securely ligatured at each end, the ligature being tied into a loop for suspension in the muscle chamber as described by Meyer.<sup>17</sup> This strip of artery will be referred to hereafter as the Meyer strip. The cannula B was then inserted into the stopper D, the Meyer strip having also been placed in the cylinder, and placing the stopper D' on the cannula B', before inserting it firmly into the cylinder, the apparatus was held vertical for a moment and the artery allowed to assume a natural position, suspended as it was from its upper end. In this way all twisting of the artery around its long axis was prevented. The stopper D' was then inserted tightly, and the cylinder put in place and filled with cold Ringer's solution from the external circulation. The internal circulation was then connected with the cannula B, the Hürthle manometer and outflow capillary with the cannula B', and Ringer's solution allowed to flow through the artery until all the air could be driven out, great care being taken that the internal circulation should never be above the pressure of the external circulation, in order that there should not be the least stretching of the vessel during this part of the procedure. Then, the coldest possible temperature being maintained in the water-jacket, a measurement of the compressibility of the tightly constricted cold artery was made. This reading and all others were made exactly as described under post-mortem arteries, the three points of the beginning of collapse of the artery, of total cessation of flow, and of the first resumption of flow as shown by the Hürthle manometer, all being recorded. Such vessels, during this part of the procedure, were of exceedingly small lumen, with rigid walls, and offered marked resistance, even to bending. These readings were made with an internal pressure of 70 mm., the obliterating pressure being so great that we were unable to obtain the necessary difference in levels between the bulbs, with the internal circulation set at any higher point.

After one or two readings were made with cold vessels, the temperature in the whole apparatus was raised to 37° C. by warming the reservoir feeding the water-jacket, and maintained, as nearly as possible, throughout the rest of the

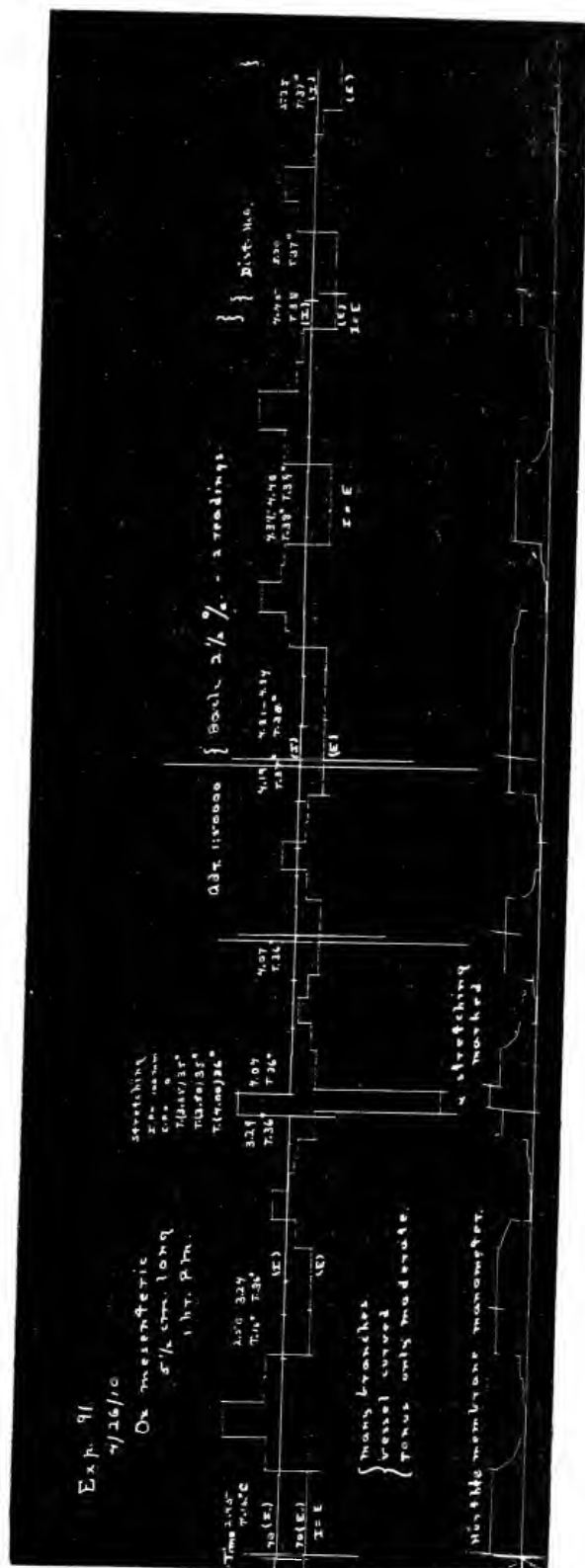


Fig. 2. Typical tracing from a surviving artery. Upper line (I): Record of manometer connected with internal circulation through artery; pressure, 70 mm. Hg. Second line (E): Record of manometer connected with external compressing circuit. Third line: Tracing from Hürthle membrane manometer connected with outflow from artery. Base line; Base line of Hürthle manometer.

experiment. As soon as the temperature had reached 37° C., a second measurement of the obliterating pressure was made.

At this point the circulations were shut off and the Meyer strip removed from the cylinder, which was then closed. Then the circulation was reopened and the outflow through the capillary closed. The pressure in the internal circulation was raised to 100 mm., and that in the external lowered to zero, and the pinch-cock on tube G opened. This subjected the artery to an internal distending pressure of 100 mm. and caused a very great increase in its diameter. At the same time, observation of the escape of fluid from the open end of the tube G served to detect any unrecognized leaks, which would vitiate the experiment. The Meyer strip was transferred at once to a muscle chamber containing Ringer's solution, kept at 37° C. by a water-bath, and connected with a light muscle lever, magnifying six times, following the exact technic laid down by Meyer. This strip was then stretched with a load of 90 gm. for carotids and 70 gm. for mesenterics, during the period of stretching of the artery in the cylinder, these loads having been found by Meyer to be sufficient to overcome completely the contracture of the vessel in fifteen minutes. After a lapse of not less than fifteen minutes, the pressures in the internal and external circulations were again brought to 70 mm., and a measurement of the compressibility of the now completely relaxed artery was made. Following this, the load on the Meyer strip was reduced to 50 gm. for carotids and 20 gm. for mesenterics, and sufficient time given to allow the artery to become adjusted to this load, as shown by the muscle lever writing a horizontal line.

The next step was the substitution for the internal circulation of Ringer's solution, of a solution of epinephrin chlorid in Ringer's solution, 1 in 100,000 or 1 in 50,000. When this had flowed through the artery for one minute, another measurement of the compressibility was made with as much expedition as possible. On its completion the Meyer strip was similarly tested, Ringer's solution in the chamber being replaced by epinephrin in Ringer's solution of equal strength to that used in the artery, and the contraction of the strip recorded on a drum. Finally an internal circulation of barium chlorid in Ringer's solution, 2.5 to 5 per cent. in different experiments, was substituted and allowed to flow through the artery for three minutes after it could be identified in the outflow by its precipitation by sulphuric acid. This considerable time was given because of our observation of the long latent period before contraction to barium chlorid in the Meyer strip. At the end of the three minutes the compressibility of the artery was again measured, and in certain cases two or three successive measurements were made. On the completion of the first, the reaction of the Meyer strip to barium chlorid was tested in the same way as to epinephrin.

By the technic described we obtained tracings such as are reproduced in Figures 2 and 3.

By measuring the increment of external pressure used to produce collapse of the artery, complete cessation of flow, and the first resumption of the flow after obliteration of the lumen of the artery, we believe we have obtained a clearer conception of the mode of compression of the vessel and have obtained results more comparable with criteria used in clinical blood pressure determinations, than have previous observers. In addition, we have determined for living ox arteries the effect on their compressibility of extreme contracture produced by cold, as compared with the compressibility of the same vessel when warmed, and when subsequently warmed and stretched to complete relaxation; also of vasoconstriction produced by epinephrin and by barium chlorid, the surviving character of the vessel in all cases having been proved by the subsequent reaction to similar epinephrin and barium chlorid solutions of a Meyer strip from the same artery, subjected throughout to identical conditions.



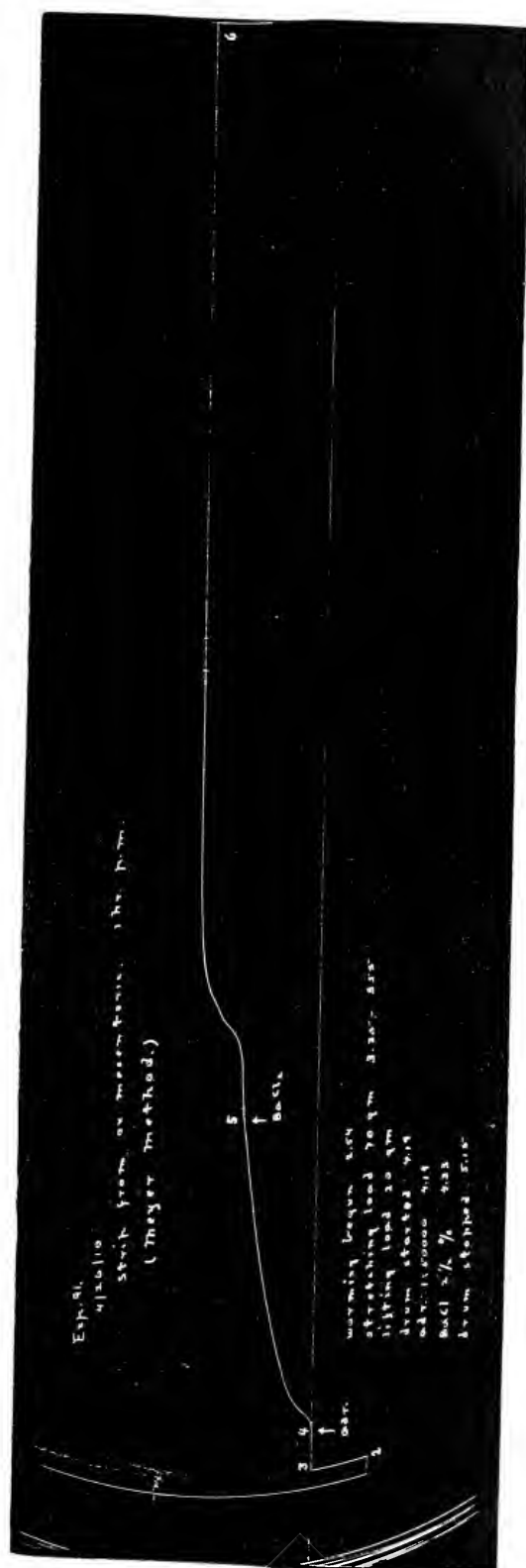


Fig. 3.—Tracing of Meyer strip control from artery of Figure 2: 1. Large fall of muscle lever during stretching with 70 gm. 2. Rise of lever on reduction of load to 20 gm. 3. Horizontal trace, showing equilibrium of strip. 4. Rapid contraction from epinephrin, 1:50,000. 5. Additional rise from barium chloride, 2.5 per cent. solution. Note latent period and persistence of contraction for forty-two minutes. 6. Gradual fall of lever during succeeding twenty-four hours, showing slow return of artery toward original length.

The technic in the case of some of the amputation vessels was the same as for the living ox arteries, but in no case have we been able to obtain a definite reaction in the Meyer strip, and we are therefore unable to predicate the surviving character of any of these human arteries. They must therefore be considered as representing unusually fresh dead vessels.

The most difficult problem connected with these arteries of the extremities is the ligaturing of their very numerous branches and the consequent excessive handling and waste of time. We do not despair, however, of being able so far to perfect our procedure as to obtain results similar to those obtained with the animal vessels.

#### SOURCES OF EXPERIMENTAL ERROR

The various sources of error, through which it became necessary to discard large numbers of experiments, were as follows:

1. *Air Locks*.—The locking of the internal circulation by a bubble of air at the mouth of the outflow cannula, or at some turn in the tubing, was a troublesome source of errors, necessitating the discarding of results in our earlier experiments. This we carefully guarded against later.

2. *Leaks in the Vessels*.—Even after careful ligation of all visible branches leakage occasionally occurred. This was due either to a minute branch concealed beneath the outer connective tissue coat, or to small holes where branches had been pulled out, and the adventitia slipped over the opening, concealing their existence; or to slipping of ligatures. The method of testing already described showed the most minute leaks, and some such test is absolutely necessary. In the case of a minute branch, allowing a very slight escape of fluid outward at an internal pressure of 100 mm. Hg, we did not consider that there could be flow in the reverse direction at a difference in pressure of only 10 or 20 mm. Hg. With all other forms of leak the experiment was discarded.

3. *Torsion of the Vessel*.—Any twisting of the vessel around its long axis is liable to introduce a very large error, though this is not constant. We are convinced that any experiment in which this possibility was not recognized and carefully guarded against cannot be accepted at all. We are inclined to believe that some of Herringham and Womack's<sup>2</sup> unintelligible results may have been due to this cause.

4. *Longitudinal Tension*.—The degree of longitudinal stretching of the artery exerted much less influence on its compressibility than did torsion, but was capable of somewhat increasing its resistance to compression, especially in the case of short vessels. Undue stretching was therefore carefully avoided.

5. *Insufficient Length*.—The length of the portion of artery examined proved a marked factor in determining its resistance to compression, as might be expected from von Recklinghausen's<sup>11</sup> demonstration of the error

introduced by the narrow arm-piece in clinical blood-pressure measurements. This influence, like that of torsion, was exceedingly variable. The following experiments, in which successive tests of different lengths of the same arteries were made, showed clearly the possibility of error from this source.

TABLE 1.—INFLUENCE OF LENGTH OF SEGMENT ON COMPRESSIBILITY

ADULTS' COMMON CAROTIDS, FORTY EIGHT HOURS POST MORTEM

Difference of pressure at which flow returned, internal pressure being 100 mm. Hg.

Exp.	—Before Shortening—		—After Shortening—	
	Length in cm.	Pressure in mm. Hg.	Length in cm.	Pressure in mm. Hg.
35	7.5	4	4	39
37	13	13	2	86
38	11	5	3.5	7
42	8	6	3	7
45	12	0.5	4	1
49	9	5	2.5	18

The inconstant occurrence of erroneous results from this, and from the previous cause, we are inclined to attribute to variations in the condition of adjacent portions of the wall in many vessels. Presumably the softest bit of wall in the length of artery examined determines the cessation of flow, rather than a uniform compression of the entire vessel; therefore a short piece of artery, if it contain a thin spot, will be as compressible as a longer one; whereas, if the thin portion happens to be cut off, the resistance to compression will be markedly altered. It seems to us probable, from observation of the mode of collapse of many arteries, that most, if not all human vessels, are of irregular thickness and compressibility, the weakest spot determining the resistance of the whole; and that long portions give the lowest readings, because more likely to contain a thin area.

In addition, there must be some resistance in the very short strips due to longitudinal strain on the indented wall, as described by von Recklinghausen.<sup>11</sup>

We feel convinced that experiments made on arteries of a less length than 5 cm. clear between the ends of the cannulas, except in the case of very small and thin-walled vessels, are altogether valueless, unless so low a reading is obtained that it can obviously contain no marked factor of error. Since Herringham and Womack<sup>3</sup> described the arteries examined by them as being from 2 to 3 inches, that is 5 to 7.5 cm. long, and since one can scarcely tie the end of the vessel over a cannula without using nearly 1 cm. of it, it seems to us probable that many of their experiments were performed on vessels much less than 5 cm. in length between the

cannulas. We are strongly inclined to attribute many of their discrepant results to this cause, though the state of contraction of the vessels examined by them may have played a considerable part.

6. *Differences in Temperature and in Composition of the Artificial Circulation.*—In the experiments on living vessels, differences of more than a degree or two in temperature either way caused us to reject the experiment completely, and we believe, as a result of a few observations, that a uniform composition of the circulating media is important. For these reasons, we take exception to the recently published experiments of Scholtyssek<sup>6</sup> and of Schmidt,<sup>7</sup> as we have already noted.

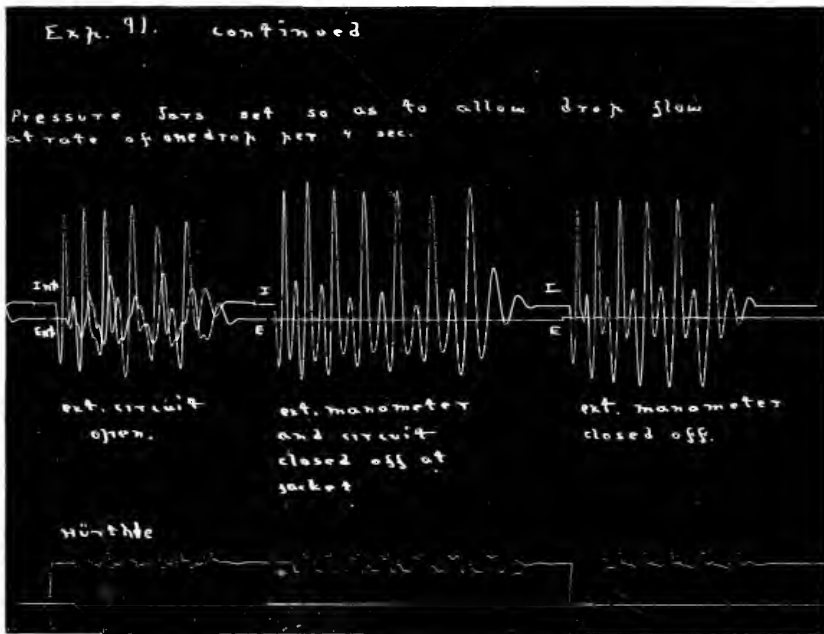


Fig. 4.—Tracing from the same experiment as Figure 2, showing a wave passing through the artery at pressure of return of flow. Both pressures as at end of Figure 2. Note different form of wave with external circuit open, allowing waves to be set up in it; with external circuit shut off at the cylinder, and last with the manometer, but not the pressure-bulb, shut-off.

Of great interest to us was the corroboration we obtained of Meyer's<sup>17</sup> statement that his vessel strips were exquisitely sensitive to traces of adrenalin, so that pipettes could not be used twice the same day. We were obliged, after losing a number of observations, to allow two days to elapse between experiments, for washing out the last traces of epinephrin and barium chlorid from our apparatus.

## TABULATION OF RESULTS

Tables 2 to 5 show the results obtained in all our successful experiments on arteries. No experiments have been included in which there was the least suspicion of technical error. For simplicity, and because we do not feel as yet in a position to discuss its significance, the manometer readings for the point of first collapse of the artery have been omitted. For the infants' carotids, complete obliteration of the artery with cessation of flow occurred with such a small increase of external pressure that no measure of the return of flow after compression was possible. In all other tables the pressure at which the flow was completely abolished, and at which it was first reestablished, as shown by the rise of the Hürthle manometer, are both recorded. In all post-mortem vessels, measurements are tabulated at three different internal pressures. The experiments on amputation vessels were carried on at an internal pressure of 100 mm., those on surviving ox vessels at an internal pressure of 70 mm.

For these vessels we have tabulated only the pressure at which the flow was reestablished through the artery. Throughout all our experiments we have found this point, which is represented by the first steady rise of the lever of the Hürthle manometer, much more constant in its behavior than the point of complete cessation of flow. The reasons for this are somewhat complex and probably dependent on the exact mode of closure of the artery and the shape of the cross-section of its lumen when compressed. In many cases, after practical collapse of the artery, the flow of a drop every five seconds to even once a minute would persist after raising the external pressure many millimeters. Studies in progress at present on this point we hope to present later. The amount of flow represented by the first rise of the Hürthle manometer was pretty regularly one drop in three or four seconds from the capillary. We are convinced that this is by far the most constant index of the compressibility of arteries. It is also without question the most analogous to the usual criterion in clinical blood-pressure measurements, the return of the pulse after obliteration.

We have made a number of observations to determine the relation which this point bears to the passage of a wave through the artery, in order to satisfy Hill's<sup>4</sup> objection to Herringham's<sup>3, 5</sup> results. Our observations on this point show that the question of the passage of a wave under the mechanical conditions of our experiment is also a complicated one. If the outer compressing medium be in continuity with its pressure-

bulb and manometer, waves are transmitted from the artery to the compressing solution, which apparently may either produce summation or interference with waves within the artery, thus either facilitating or hindering their passage. By clamping off the connection with the pressure-bulb this element could be obviated. Under these conditions, waves with the maximum pressure, that of the previous internal pressure used in the experiment, did not come through at a pressure above that of the return of the flow. At this point a slight wave was transmitted. While it would be impossible to investigate all the conditions surrounding the passage of a wave, we feel that the index which we have used, the pressure at which the flow is first reestablished after compression of the vessel, can be accepted as the closest approximation to the clinical criterion of the return of the pulse-wave after obliteration. Figure 4 shows the different forms of wave passing through the artery, with different conditions for participation in the wave motion by the external circulation.

TABLE 2.—TEN INFANTS' CAROTIDS

Exp.	Length in cm.	Time Post Mortem. in Hours.	Difference of Pressure in mm. Hg, at which Flow Ceased		
			Internal Pressure.		
			30 mm.	100 mm.	150 mm.
1	7	10	1	1	3
2	6	8	1	3	4
3	4	28	2	3	3
7	5	18	2	3	6
10	5	3	3	5	5
11	6	6	6	6	7
12a	4.5	59	1	3	5
13a	6	6	2	4	5
14	4.5	6	5	8	8
24	6	1	4	4	..
			Av. = 2.7	4	5.1

SUMMARY OF RESULTS OF ALL EXPERIMENTS

Maximum difference.....	8 mm.
Average difference.....	3.9 mm.
Minimum difference.....	1 mm.

TABLE 3.—TWENTY ADULTS' CAROTIDS

ALL EXAMINED MORE THAN FORTY-EIGHT HOURS POST MORTEM

Exp.	Group.	Length.	— Difference of Pressure in mm. Hg, at which Flow — Ceased					
			Returned	Ceased	Returned	Ceased	Returned	Ceased
			Int. P.	30 mm.	Int. P.	100 mm.	Int. P.	150 mm.
22	B	9	8	6	10	3	6	2
23	B	9	12	5	..	..	10	3
29	A	9	30	14	28	16	24	16
30	A	7	26	18	22	19	23	19
31A	A	8	18	12	24	14	18	9
32	A	11	18	10	16	11	16	8

TABLE 3.—TWENTY ADULTS' CAROTIDS—Continued

Exp.	Group.	Length.	— Difference of Pressure in mm. Hg. at which Flow —					
			Ceased	Returned	Ceased	Returned	Ceased	Returned
			Int. P.	30 mm.	Int. P.	100 mm.	Int. P.	150 mm.
33	A	8	22	12	20	12	20	11
34	A	11	13	6	14	8	16	9
35	A	7	17	13	16	8	19	14
36	A	11	14	6	16	6	12	7
37	A	13	14	12	20	13	11	12
38	B	11	10	6	13	5	11	9
39	A	8	9	2	10	1	8	0
41	A	8	16	10	12	8	10	7
42	A	13	13	6	11	6	12	6
45	A	12	3	0.1	3	1	6	2
46	A	11	..	..	11	6	..	..
47	C	4	28	10	25	14	20	10
48	A	7	19	11	15	9	15	6
49	A	9	16	6	8	5	12	4
Av. = 16.1				8.7	15.5	8.7	14.1	7.6

## SUMMARY OF RESULTS

Group.	No. of Arteries.	Condition.	Difference of Pressure at which Flow: —	
			Ceased.	Returned.
A	16	Slightly atheromatous	Maximum 30 Average 15.6 Minimum 3	19 8.7 0
B	3	Moderately atheromatous	Maximum 13 Average 10 Minimum 6	9 4.9 2
C	1	Calcified	Maximum 28 Minimum 20	14 10

TABLE 4.—FOUR ARTERIES FROM AMPUTATIONS

Exp.	Artery.	Condition.	Length cm.	Hours After Removal.	Age of Patient.	Temp. C.	Difference of Pressure at which Flow: —	
							Ceased.	Returned.
43	Femoral	Normal	7.5	2	24*	37	4	3
44	Post. Tibial	Calcified	11	2	58†	37	24	11
73	Femoral	Normal	7	1	40‡	15	21	16
						37	16	6
						§37	11	2
						¶37	22	10
92	Femoral	Extremely calcified	8	1½	65‡	18	34	17
						36	32	17
						§36	28	16

\* Sarcoma.

† Diabetic gangrene.

‡ Osteomyelitis.

§ Stretched.

¶ Barium chlorid.

TABLE 5.—SURVIVING ARTERIES

## SEVEN OX CAROTIDS

Difference of pressures at which flow returned at the different stages of the experiment.

Exp.	15 C.	37 C.	Stretched.	Epinephrin.	Barium Chlorid.
72	25	13	9.5	10.5	28.5
75	68.5	14	8	10	15.5
81	50	14	5	7	18.5
82	57	22	6	9	13.5
83	29	8	4.5	8	11
84	39	15	7	7.5	9
90	31	14	6	10	12.5
Maximum . .	68.5	22	9.5	10.5	28.5
Average . . .	42.8	14.3	6.6	8.9	15.5
Minimum . .	25	8	4.5	7.5	9

## FOUR OX MESENTERICS

Exp.	15 C.	37 C.	Stretched.	Epinephrin.	Barium Chlorid.
85	52	8	4	6.5	55
86	14	4	4.5	6	18
89	10.5	5	2	6	20
91	24	9	5	8	25
Maximum . .	52	9	5	8	55
Average . . .	25.1	6.5	3.8	6.6	29.5
Minimum . .	10.5	4	2	6	18

## DISCUSSION OF RESULTS

1. *Influence of Varying Internal Pressure.*—In our first fifty experiments we considered it important to test the compressibility at different internal pressures, 30, 100, and 150 mm. being used. A glance at the results, especially as given in Table 3 for the adults' arteries, shows that the difference at these several internal pressures was altogether negligible. Since the experiments on the surviving ox vessels required the use of such great differences in pressure that the internal circulation had to be maintained at 70 mm. Hg. on account of the limited height of our room, it became imperative to make sure that, for living vessels also, their compressibility did not vary with changes in the internal pressure. The experiment summarized in Table 6, performed on a surviving ox carotid completely relaxed by stretching at 37 C. demonstrates quite clearly that the height of the internal pressure, under the conditions of our experiments, is without influence on the compressibility of the vessel. The slight differences observed in this experiment are within the limits of experimental error.



TABLE 6.—INFLUENCE OF VARYING INTERNAL PRESSURE

Int. Pressure in mm. Hg.	EXPERIMENT 93 Difference of Pressure in mm. Hg at which Flow:	
	Ceased.	Returned.
20	11.5	4
40	12	4
60	10	4
80	9	4
100	12	6
120	9	5
140	9.5	5.5
160	10	5

2. *Influence of the Thickness of the Arterial Wall.*—Comparative experiments in which the influence of the wall thickness on the compressibility could be tested without complication by any other factor were not attempted. The thickness of the wall varies either directly with the size of the lumen of the vessel or with the state of contraction of its musculature. For this reason the most that can be demonstrated is the combined effect of the thickness of the wall and the size of the artery. This stands out clearly on comparison of the results obtained from the infants' arteries and from the adults' common carotids. A glance at the summary of Tables 2 and 3 shows at once that the small and thin-walled infants' vessels can be completely obliterated by very low pressures, the maximum, average and minimum in all cases lying far below those for adult arteries. The point of resumption of flow was not even measurable with these small vessels, so that only the pressure necessary to produce complete obliteration of the artery was recorded. It seems, therefore, quite evident that, for children's vessels, the resistance to compression of the arterial wall does not exist as a practical source of error in clinical blood-pressure work.

We believe that the influence of these combined factors may be seen by comparing the results for the ox carotids and ox mesenterics, when warmed and stretched. In this condition tonus was abolished, and the greater pressure of 2.5 to 4.5 mm. necessary to obliterate the carotid must be definitely related to its thicker wall and larger caliber.

We therefore feel justified in affirming that, other things being equal, the thicker the wall of an artery the greater is the resistance which it offers to compression.

3. *Influence of Disease of the Arterial Wall.*—While it is practically impossible to study the effect of arteriosclerotic changes on compressibility, uncomplicated by other factors, certain conclusions seem justified from our experiments on adult human vessels from autopsies and amputations. The vessels examined, with the exception of two amputated femorals, all showed slight fatty patches in the intima. These two wholly

normal arteries showed a return of flow, respectively, at 3 mm. and 2 mm., overpressure in the external circulation. These are, of course, altogether negligible quantities. The remaining arteries could be divided into those showing slight atheroma, those showing moderate atheroma with numerous patches of intimal thickening, and those showing calcification.

*Atheroma.*—A comparison of the results shown in the summary of Table 3 shows at once that the variation within the group of slightly atheromatous arteries was very great, and that the highest individual readings were above any obtained with much more diseased vessels, and were even higher than the figures for the single calcified post-mortem artery. It is therefore obvious that, whatever influence on compressibility may be exerted by atheroma, it is so far subordinate to the influence of some other factor or factors as to be indistinguishable in our experiments. The other factor, we think we shall demonstrate later, is the state of contraction of the arterial wall. Since one moderately atheromatous vessel gave a reading as low as the lowest normal artery, one hour after amputation and completely stretched at 37° C., we feel that it is probably justifiable to conclude that atheromatous changes are practically without influence on the compressibility.

*Calcification.*—It is generally supposed that arteries showing advanced calcification exhibit the most marked resistance to compression. This belief seems altogether reasonable, since, when such vessels are removed and squeezed in the fingers, they feel hard and brittle, and can be compressed only by actual fracture of the chalky plates in their walls. The not infrequent observation of low blood-pressure readings in persons who have nodular calcified brachials, has convinced us in the past that such is not always the case. We were able to examine three arteries showing the most extreme degree of calcification, one post-mortem common carotid, and two from amputations for diabetic gangrene (Experiment 44), a posterior tibial (Experiment 93) and a femoral. Table 7 shows the results of all observations on these vessels.

TABLE 7.—SUMMARY OF ALL OBSERVATIONS ON THREE ARTERIES, SHOWING MARKED CALCIFICATION

	Difference of Pressure in mm. Hg	
	— at which Flow: —	
	Ceased.	Returned.
Maximum . . .	34	17
Average . . .	27.7	14.2
Minimum . . .	20	10

It is evident that the average pressure required to compress these vessels was 5.5 mm. above the average for the slightly atheromatous post-mortem vessels. The minimum was strikingly higher, 10 mm., while the

maximum was actually 2 mm. below the highest reading from an artery with almost normal wall. It is, therefore, again evident that even calcification of the most extreme degree has less influence on the compressibility of the arterial wall than some other factor or factors. The complete explanation of this we hope to obtain by a study of sections taken at different points of these compressed vessels, which we expect to report later. From our rough observation of the behavior of these arteries, however, we think it probable that no such vessels will be found calcified throughout their whole circumference for any considerable distance. It is altogether unlikely, therefore, that any strip of such a vessel, as much as 10 cm. long, should fail to have soft and uncalcified spots in its wall. Such soft spots may be easily compressed against a calcareous plaque on the opposite side of the vessel—in fact, almost as easily as the normal brachial artery may be flattened out against the humerus. The inspection of these vessels, while undergoing compression, has shown collapse of the vessel in a small area while the rest still stood open, and has convinced us that the foregoing explanation accounts for the apparent disparity between their behavior under the finger and in our apparatus. The importance of examining a segment of sufficient length is greatest in the case of these calcified vessels, and the need for the broad arm-piece in clinical work is emphasized from a new standpoint.

It seems safe to conclude that calcification of the arterial wall distinctly increases its compressibility; that the error introduced in this way probably never exceeds 20 mm., and is usually 10 to 15 mm.; and that this error is less than may be found from other causes in vessels altogether free from calcification.

4. *Influence of Tonus.*—Our studies of surviving arteries from the ox seem to us to demonstrate beyond doubt the predominant importance of the state of contraction of the arterial wall as a factor in determining its compressibility. A glance at the tabulation of these results shows the enormous resistance to compression of the tightly contracted cold arteries. With the relaxation of the wall, produced by warming to body temperature, compressibility is greatly increased, the average fall in pressure obtained in this way being 28.5 mm. for the carotids and 18.6 mm. for the mesenterics. On further stretching to complete relaxation, the arteries could be compressed by comparatively small increments of external pressure. The greatest difference is seen in one carotid (Experiment 15), which required 68.5 mm. overpressure when cold, only 8 mm. when warmed and stretched. No mesenteric artery, when warmed and stretched, required more than 5 mm., and no carotid more than 9.5 mm. overpressure.

The most unequivocal results, however, were those obtained after the introduction of epinephrin, and then of barium chlorid, into the relaxed arteries. Any change in the resistance to compression produced by these substances, which, simultaneously, evoked a strong contraction of the Meyer strip, must be attributed solely to increased tonus. The effect of such tonus is shown in Table 8.

TABLE 8.—INCREASED RESISTANCE TO COMPRESSION IN MM. HG PRODUCED BY EPINEPHRIN AND BARIUM CHLORID

IN SEVEN SURVIVING OX CAROTIDS		
	Epinephrin.	Barium Chlorid.
Maximum .....	4	19
Average .....	2.3	8.9
Minimum .....	0.5	2
IN FOUR SURVIVING OX MESENTERICS		
	Epinephrin.	Barium Chlorid.
Maximum .....	4	51
Average .....	2.8	25.6
Minimum .....	1.5	13.5

The constriction produced by barium chlorid was much greater than that produced by epinephrin, and very much more lasting. The contraction of the artery was often easily visible. In Experiment 85 the extreme rise of 51 mm. was so far beyond the next highest rise for the mesenterics of 20 mm., in Experiment 91, that the question of some undetected error was raised at once. We were unable to discover any source of error and therefore did not feel justified in discarding the result merely because it seemed so extreme.

Another interesting fact, which seems clear from our experiments, is the distinctly greater tonus we were able to evoke in the mesenteric arteries, as compared with the carotids. The latter are, of course, more elastic and less muscular vessels, and with their thicker walls, showed a uniformly higher reading in the relaxed state than did the former. It seems altogether reasonable that they should show a slighter response to vasoconstricting agents.

From these experiments on surviving ox arteries we feel that the conclusion is inevitable that the tonus of the arterial wall is by far the most important factor capable of influencing its resistance to compression, and that marked tonic contraction of the artery examined may introduce a considerable error in the clinical measurement of blood-pressure. We do not feel in a position, from the small number of successful experiments thus far attained, to set a numerical limit to this error. The carotid of the ox is a decidedly heavier vessel than the human brachial artery and, in point of size and thickness of wall, the mesenteric is more analogous.

If the single extreme result from barium chlorid be omitted, we have no figure above 28.5 mm. It seems to us rather unlikely that any degree of contraction of human arteries during life can surpass that which we have obtained with a 2.5 per cent. solution of barium chlorid, and altogether inconceivable that anything approaching the condition of the rigidly contracted cold arteries should ever occur in the body. It therefore seems to us reasonably proved that Russell's<sup>13</sup> contention that hypertonic contraction of the arteries, and not high blood-pressure, is the cause of the high readings obtained with clinical instruments, has no basis in fact. On the other hand, we must acknowledge that Russell has called attention to a heretofore insufficiently recognized influence of arterial contraction on our clinical readings. Further studies on different vessels and different animal species will be necessary to settle finally the exact extent of error from this source.

Because of these striking evidences of the effect of contraction of the arterial wall on its compressibility, we are of the opinion that herein lies the chief explanation of Herringham and Womack's<sup>3</sup> otherwise unintelligible results. MacWilliam and Mackie<sup>15</sup> have already pointed out the probability of this. Herringham<sup>5</sup> considered that his subsequent sodium fluorid experiment sufficiently answered them, but here altogether foreign conditions were introduced. Arteries after death may evidently pass into a condition of more or less extreme contraction, and require prolonged stretching to overcome it. Such differences between the two brachial arteries, or the carotid and iliac from the same patient, are most easily explicable on the assumption that, because of unequal chilling, or for other causes, one artery became more contracted after death than the other.

As additional evidence of death of an artery in extreme contraction, we would cite an observation made on a surviving ox carotid, allowed to die in position in the apparatus without removal of the barium chlorid with which the last reading was made. The result was as given in Table 9.

TABLE 9.—EFFECT OF DEATH OF ARTERY IN TONIC CONTRACTION  
Experiment 75: Ox carotid; Int. Circ.: 2.5 per cent. BaCl<sub>2</sub>.

Hours After Removal.	Difference of Pressure in mm. Hg at which Flow:—	
	Ceased.	Returned.
7	36	15.5
28	74	31

This artery, on examination, felt wholly altered and resembled rubber tubing or a boiled artery.

## THE RESISTANCE TO COMPRESSION OF OTHER ELASTIC TUBES

A study of all the conditions determining the compressibility of elastic tubes, while it would be most illuminating, involved the solution of more intricate physical problems than we were competent to pursue. The whole conception of elasticity as manifested by the arterial wall, of which compressibility is but one aspect, is greatly in need of clarification; but the practical object of our investigation seemed attainable without a determination of all the underlying causes for our results.

Russell,<sup>19</sup> however, after adducing some rough observations on rubber tubing in an artificial circulation scheme, in support of his contentions, makes the following remarkable statement:

Objection has been taken to these results on the ground that arteries are not rubber tubes. I have made some observations with vessels obtained from the post-mortem room, and, so far as I have yet carried these, they seem quite worthless, for the simple reason that the dead vessel no longer possesses the tone or the elasticity of the living vessel. In fact, the rubber tube is a better substitute for the living artery than the dead one is.

Such an affirmation seemed to challenge criticism and to be well worth a few real observations to prove or disprove. We therefore tested rubber tubing of varying thickness of wall and caliber, by the same method used for arteries. Not a single sample of tubing could be compressed sufficiently to abolish flow, with the pressure available in our apparatus, hence the point of return of flow could not be observed.

The results are shown in Table 10:

TABLE 10.—RUBBER TUBING

Exp.	Type.	Difference in Pressure			Flow.
		Wall.	Lumen.	in mm. Hg.	
26	Black	2	7.5	150	Unchanged
26A	Black	2	5.5	152	Unchanged
26B	Black	2	4.5	152	Unchanged
26C	Black	1.3	3.5	152	Unchanged
26D	Black	1	3	152	Slightly diminished
94	Red	1	6	148	Reduced to 1 drop in 2 seconds

The tubing selected was the newest and softest obtainable. The smallest we could secure was of thinner wall and smaller lumen than the ox carotids. In the latter, of course, all measurements were wholly relative, depending on the degree of contraction. A vessel which, when cold has a scarcely appreciable lumen and a wall several millimeters thick would, after warming and stretching, have a much thicker wall and a lumen of more than a centimeter. Definite comparison, however, can be

19. Russell, W.: Arterial Hypertonus, Sclerosis and Blood-Pressure, J. B. Lippincott Co., Philadelphia, 1908, p. 60.

made with a few of the post-mortem vessels from Table 3, all showing but little atheroma, which we measured. These showed the following striking contrast:

TABLE 11.—ARTERIES COMPARABLE IN SIZE TO RUBBER TUBING

Exp.	Wall mm.	Lumen mm.	Difference of Pressure in mm. Hg at which Flow Ceased.
32	1	6	18
33	1	7	22
34	1	7	13

In all the experiments on surviving arteries, after the primary contracture had been overcome, the complete cessation of flow was produced by pressures not more than 10 mm. above those tabulated for the return of flow, that is, always below 20 mm. With epinephrin tonus their compressibility was not very different, the complete obliteration of the lumen occurring below 30 mm. This is scarcely good evidence that the rubber tube, incompressible at 150 mm., "is a better substitute for the living artery than the dead one is."

The surviving arteries when first examined, cold and rigidly contracted, reacted more like rubber tubing, though none of these failed to compress at 150 mm. Such a condition, of course, is in no way comparable to anything possible in the living body.

Under the influence of barium chlorid the pressure needed to abolish flow completely was at times surprising great, as compared with that at which flow returned. This difference seems worth recording, though all the reasons for it are not yet clear.

TABLE 12.—SURVIVING OX ARTERIES WITH BARIUM CHLORID

Exp.	CAROTIDS	
	Difference of Pressure in mm. Hg at which Flow:	
	Ceased.	Returned.
72	46	28.5
75	36	15.5
81	88	18.5
82	34	13.5
83	22	11
84	18	9
90	45	12.5

Exp.	MESENTERICS	
	Difference of Pressure in mm. Hg at which Flow:	
	Ceased.	Returned.
85	104	55
86	27	18
89	46	20
91	40	25
Average..... 46		20.6

Even these figures are in no way comparable to the resistance of rubber tubes, though they emphasize the complex relations of arterial compressibility. We do not believe that they in any way represent vital conditions, or that they have any applicability to the practical problem outlined for this research. The flow which occurred between the point which we have used as our index and the pressure necessary to compress the artery completely was always a minimal one, by drops. We have convinced ourselves that, throughout this range of pressure, no pulse-wave can pass. It, therefore, in our opinion, represents the persistence of a chink at the outer end of the flattened arterial lumen, through which an occasional drop may escape, and requiring high pressure to squeeze together absolutely. This we also hope to demonstrate later by sections of such arteries during compression. Practically, only the pressure at which flow returns is comparable with the conditions of clinical blood-pressure measurement. Furthermore, we question whether any artery during life exhibits such constriction as is produced by strong barium chlorid solutions.

The only method by which we have been able to make arteries react like rubber tubes is by boiling them. A large common carotid which compressed at 9 mm. one day and at 13 mm. the succeeding day, after boiling for one minute became incompressible at 164 mm. This was a post-mortem artery certainly, but scarcely what Russell had in mind in making his comparison. This immediate and complete alteration of the physical character of an artery by short exposure to high temperature, seems to us only to emphasize the essential difference between the arterial wall during life, or for a reasonable time after death, and India rubber.

Two other structures examined by us may be mentioned briefly in closing. An infant's esophagus was tested and found to compress absolutely at an increment of external pressure of only 1 mm. Hg. This clearly represents the other extreme, a muscular structure with the minimum of connective and elastic tissues, and yielding at once to any deforming force. The intestine was also tested, but fruitlessly, since its lax wall at once collapsed over the end of the outflow cannula.

#### CONCLUSIONS

1. The arterial wall offers definite resistance to compression.
2. Other things being equal, small arteries with thin walls are more readily compressed than large arteries with thick walls.
3. In infancy and childhood the resistance of the arterial wall is a negligible factor in clinical blood-pressure measurements.



4. Arteries as large as the brachial may require only the pressure of a few millimeters of mercury for the obliteration of their lumen.

5. In adults with normal arteries and a normal range of blood-pressure, the arterial wall is a practically negligible factor. It probably never introduces an error greater than 10 mm. Hg in clinical blood-pressure measurements, a figure less than the spontaneous variations in pressure from minute to minute.

6. Atheroma, even of considerable degree, is without appreciable effect on the compressibility.

7. Calcification of the arterial wall, when segments longer than 6 cm. are examined, increases only moderately its resistance to compression. The overpressure dependent on this factor in our experiments did not exceed 17 mm. Hg.

8. In clinical blood-pressure determinations, if a wide arm-piece be used, and the return of the first fully developed pulse-wave be taken as the index, as recommended by von Recklinghausen, even advanced arterial thickening and calcification probably do not introduce an error of any importance.

9. The only factor determining the compressibility of an artery which seems capable of introducing an error of real importance in the clinical measurement of systolic blood-pressure, is the state of contraction of its walls. It is impossible from our experiments on surviving ox arteries to set definite numerical limits for this in man. From these experiments, however, combined with our study of human arteries, after amputation and post mortem, we feel that a degree of hypertonic contraction of the brachial artery sufficient to cause an error of more than 30 mm. Hg seems improbable, and of more than 60 mm. incredible, during life.

10. The point of return of the pulse after obliteration, not of its disappearance during compression, should always be the criterion of systolic blood-pressure.

## CUTANEOUS TESTS WITH CORN EXTRACTS IN PELLAGRINS

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The zeistic theory of pellagra as enunciated by Lombroso<sup>1</sup> and von Babes<sup>2</sup> that "pellagra is to be considered as a chronic and periodically recurring intoxication which is due to a specific substance formed in more or less spoiled corn," is founded more on statistical evidence than on clear-cut experiments. Lombroso and subsequent workers, it is true, isolated from corn toxic products which had some action on the nervous system of dogs, and von Babes and Manicatide claim to have prevented this action in rabbits by injection of blood serum from a cured pellagrin. On the other hand, comparatively little has been done to test the sensitiveness of pellagra patients themselves to substances derived from corn.

If the zeistic theories of pellagra were correct, it seemed possible that the chronic corn intoxication presupposed by Lombroso and von Babes might be accompanied by a condition of anaphylactic hypersensitiveness to products derived from corn, or perhaps only from spoiled corn. The present series of observations was undertaken accordingly with a view to determining the presence or absence of such sensibility.

Von Pirquet has demonstrated that the cutaneous reaction affords the most delicate means of testing anaphylactic sensitization in man to tuberculin and other substances. Quite recently Rufus Cole and W. S. Thayer were able to demonstrate hypersensitization to buckwheat infusion in a case of fagopyrismus reported by H. L. Smith.<sup>3</sup> They found that if a drop of buckwheat extract were rubbed into a portion of the skin from which the epidermis had been removed by scratching, an urticarial wheal and general constitutional symptoms appeared within half an hour.

Since certain analogies between pellagra in man and fagopyrismus in animals had been recognized for decades, it seemed possible that a

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1. Lombroso, C.: *Die Lehre von der Pellagra, aetiologische, klinische und prophylaktische Untersuchungen*, Transl. by H. Kurella, Berlin, 1898.

2. v. Babes, V. and Sion, V.: *Die Pellagra*, Nothnagel's Handbuch der spezielle Pathologie und Therapie, Vienna, 1901.

3. Smith, H. L.: Buckwheat Poisoning, with Report of a Case in Man, *THE ARCHIVES INT. MED.*, Chicago, 1909, iii, 350.

similar anaphylaxis to corn products might be met. It seemed also possible that in pellagrins such a reaction, if positive, might also prove of importance for the diagnosis of pellagra.

In these observations cutaneous tests were made with substantially the same technic as that employed by von Pirquet,<sup>4</sup> in tuberculosis except that corn extracts were substituted for tuberculin in making the test.

The procedure was as follows: Twenty gm. of corn was extracted with 50 c.c. of ether, alcohol, 10 per cent. sodium chlorid, or 0.2 per cent. sodium hydroxid. The extract was filtered and 1-10 vol. 5 per cent. phenol added to the clear filtrate so as to give it a content of 0.5 per cent. phenol. The ethereal extracts were allowed to evaporate at 46°, until the odor of ether had disappeared.

The site chosen for the test was on the patient's wrist in an area which was subject to pellagrous pigmentation, thickening or desquamation, and, in most cases, was bare so as to be exposed to the action of light. A drop of the extract to be tested was placed on the skin and a pin-head area of epidermis beneath the drop was excoriated by the torsion of a von Pirquet stylet. Into this excoriated area the extract was rubbed with a glass rod. A series of epidermal punctures were made in this way in a line across the wrist, with another line of duplicate punctures above them. In each series there was a pair of controls in which only the pure sodium chlorid or sodium hydroxid solution or alcohol was placed on the skin.

Within half an hour after the puncture a small red or sometimes blanched areola and occasionally a small papule formed about the site of inoculation, but in only one case did these exceed 5 mm. in size, and no differences could be noted between the areas about the punctures with corn extracts and the controls. The reactions in sites which were nearest the midline of the forearm were often slightly more marked (areolæ about 1 mm. larger than the rest), but these reactions were always quite as marked with the control fluids as with the extracts and hence were of little significance.

The reactions, which were regarded as negative in all cases, consisted of simple traumatic reactions, were watched for about half an hour and the sites of inoculation were again inspected three hours, twenty-four hours, and forty-eight hours later, as well as at frequent intervals between and after the expiration of these periods.

Extracts were made from samples of good corn, spoiled corn taken from the Arkansas Insane Asylum at the time of a pellagra outbreak, and a sample of spoiled corn containing *Aspergillus fumigatus*. The

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4. v. Pirquet, C.: Tuberkulindiagnose durch cutäne Impfung. Berl. klin. Wehnschr., 1907.

extracts of the latter were filtered through a Berkefeld filter in order to avoid the danger of inoculating the skin with *aspergillus*. Other extracts were made from the apparently excellent corn-meal used at the Peoria State Hospital for the Insane at the time that the pellagra was breaking out throughout the asylum, and when a number of cases of acute pellagra were developing. Tests were made in thirteen cases of well-defined pellagra diagnosed by Dr. George A. Zeller and confirmed by Drs. Singer and MacNeal of the Illinois Pellagra Commission.

These reactions were all negative. Just before leaving Peoria a sample of spoiled corn was obtained which had been rejected from the Asylum and sent out to the hog farm over a year previously. Extracts of this corn were inoculated into six patients with subacute pellagra. The effects were observed for three hours after inoculation, but only negative reactions resulted.

In order to determine whether the presence of antibodies formed in a previous attack of pellagra might cause the reaction to be given by persons who had been afflicted with the disease in the previous year but who were free from symptoms at the time of inoculation, observations were made on seven such patients. In all cases the results were negative.

The results of these tests, therefore, render it improbable that pellagra is due to or accompanied by a condition of hypersensitiveness of the individual to products derived from good or from spoiled corn.

I take pleasure in expressing my thanks to Dr. George A. Zeller and the Illinois Pellagra Commission for placing at my disposal the patients and laboratory of the Peoria State Hospital, as well as to Dr. Carl Alsberg of the Bureau of Plant Industry, for furnishing samples of good and of spoiled corn.

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## THE ESTIMATION OF CHLORIDS IN THE STOMACH CONTENTS FROM NORMAL AND FROM ATROPHIC INFANTS\*

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The observations recorded in this paper are a continuation of work briefly alluded to in a previous article.<sup>1</sup> The purpose of this work is to discover whether or not the hydrochloric acid of the gastric juice is diminished in cases of infantile atrophy.

In the article on the causation of atrophy referred to above, I suggested a theory of the cause of infantile atrophy based on the results of secretin determinations in atrophic and well-nourished infants.

The secretin production from the cases of atrophy which I examined was much diminished compared with that from a limited number of well-nourished infants. The explanation for this diminution in secretin in atrophic infants was sought for higher up in the digestive tract. It seemed improbable that the condition was a primary one in the small intestines. The normal stimulus, according to Bayliss and Starling, which causes the transformation of prosecretin into secretin is supplied by the hydrochloric acid of the gastric juice. It was possible theoretically that the stomachs of atrophic infants secreted a diminished amount of hydrochloric acid and in consequence failed to produce an adequate stimulation of the duodenum. Most of the secretin, according to Bayliss and Starling, is produced in the upper portion of the small intestines. Only a constant and marked diminution in the amount of hydrochloric acid secreted by the stomach would have any value in support of the theory. In any case, the determination of hydrochloric acid was but a link in the chain. The cause for a constantly diminished production of hydrochloric acid by the stomach would have to be sought.

In the first series of observations, the stomach contents were obtained one hour after eating from a limited number of atrophic infants fed on

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\* From the Laboratory of Biological Chemistry of the Harvard Medical School. The expenses of this research were defrayed in part by a grant from the Proctor Fund for the Study of Chronic Diseases.

1. Wentworth, A. H.: The Cause of Infantile Atrophy Deduced from a Study of Secretin in Normal and Atrophic Infants. *Jour. Am. Med. Assn.*, 1907, xlix, 204.

mixtures of cows' milk. The determinations were made by Sjöquist's method.<sup>2</sup> The results showed a diminished amount of hydrochloric acid in the stomach contents in every case. The same series of observations included determinations of hydrochloric acid in the stomach contents from a limited number of well-nourished and apparently healthy infants fed on mixtures of cows' milk. The results in these cases were variable. In four cases the amount of hydrochloric acid was much greater than in the cases of atrophy. In three cases the amount of hydrochloric acid approximated that of the atrophic infants. As these results were not conclusive, a second series of observations was made with a view to controlling the first series. The same method of analysis was employed.

This article gives the results from the second series of observations and some conclusions that may be drawn from them.

#### METHOD OF DETERMINATION

The modified Sjöquist method for the determination of hydrochloric acid in the stomach contents was employed in these analyses. It has been stated that this method is inaccurate when the diet consists of milk because an unknown quantity of the phosphates which are present in the milk combines with some of the hydrochloric acid to form an insoluble compound that remains in the filter-paper when the barium chlorid is extracted with hot water. This has no particular importance so far as my work is concerned, because I wished to determine whether there was a constant and marked diminution of hydrochloric acid in the stomach contents from atrophic infants compared with that from healthy infants. Such differences to be of value would have to be large enough to place them well beyond the range of error in the method.

Unfiltered stomach contents were used in every case. The stomach contents were preserved in a frozen condition until the analyses could be made. Soft rubber catheters, No. 19 to No. 25 (French) were used to obtain the contents. The solid tips were cut off and in addition a large oval opening was made in one side about one-half an inch from the tip. The edges of these openings were rounded off by heat. The contents were obtained with the infant lying on its side. The quantity of contents obtained does not necessarily correspond to the quantity present in the stomach. In some cases the lumen of the tube becomes obstructed by curds; in other cases the presence of much mucus prevents the contents from being expressed. In a few instances there was every reason to

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2. Sjöquist: *Ztschr. f. klin. Med.*, 1897, xxii.

believe that the stomach contained a much larger quantity of fluid than was obtained, and yet there was no evidence of obstruction of the catheter by curds or by mucus.

I have arranged in the form of tables what I believe to be the essential data derived from these observations. This method of arrangement facilitates comparison.

The diagnosis of infantile atrophy was made from clinical evidence alone. Most of the cases were under observation for several weeks.

TABLE 1.—QUANTITATIVE ESTIMATION OF HYDROCHLORIC ACID IN THE GASTRIC CONTENTS OF INFANTS \*

ATROPHIC INFANTS											
Name.	Age in Months.	Weight.			Food Per Cent. of.			Quantity.		Free HCl†	Gm. of HCl in 100 c.c. of Gastric Contents.
		Gm.	Lbs.	Oz.	Fat.	Sugar.	Proteid.	Oz.	No. Feedings.		
A.....	4.5	3690	8	2	3	6	1	4	8	0	.01
B.....	3.5	2300	5	0	3	6	1	2.5	10	0	.016
C.....	3.5	3410	7	8	3	6	1	2.5	10	0	.012
D.....	9	3990	8	12	3	6	1	4.5	8	0	.02
E.....	3.5	4030	8	14	3	6	1.25	4	8	0	.041
F.....	3.5	4150	9	2	3	6	1	...	..	0	.07
G.....	15	7550	16	10	‡	..	....	8.5	5	0	.018
H.....	15	6830	15	..	§	..	....	8	6	0	.01+

WELL-NOURISHED INFANTS											
K.....	7.75	6390	14	..	—Milk—		....	6	6	0	.16
L.....	8	6780	14	15	4	7	1.25	8	6	*	.145
M.....	6	5900	13	..	3.5	7	1.8	6	6	*	.144
N.....	8	6950	15	5	4	7	1.5	6	6	0	.165
O.....	7	5540	11	3	4	7	1.25	5	8	0	.045
P.....	5	5180	11	6.5	3.5	6	1.8	6	6	0	.015
R.....	8	7350	16	3	4	7	1.26	6	7	0	.01+

E and F, although much under weight, were not typical cases of atrophy. Neither their previous history nor their appearance corresponded to atrophy.

‡ Milk, 7 oz.; oat jelly, 1.5 oz.

† Faint reaction.

§ Milk, 4 oz.; barley jelly, 4 oz.

† The reaction in the atrophic infants was faintly acid, in the well-nourished infants, acid.

\* From article in Jour. Am. Med. Assn., 1907, xlix, 204.

TABLE 2.—QUANTITATIVE ESTIMATION OF HYDROCHLORIC ACID IN THE GASTRIC CONTENTS OF INFANTS

## ATROPHIC INFANTS

No.	Name	Date	Age	Weight Gm.	Food.		Feed- ings. in 24 Hours.	Quantity e.c. Each Feeding.	Stomach Contents.			Remarks.	
					Approximate Per Cent. of	Pro-			Ob- tained After Feeding, Hour.	Quantity Obtained, e.c.	Chlorin in 100 e.c.		
					Fat.	Sugar.	tein.						
1	J. McH.	1/27/08	2 mos.	3010	{ 12 % cream, 150 e.c. Whey..... 600 e.c.			10	75	1	25	.004	.....
2	A. B.	12/14/07	6+ mos.	3780	3, 6, 1.			8	105	2¼	22	.03	No gain in weight for 7½ weeks.
	A. B.	12/16/07	6+ mos.	3790	3, 6, 1.			8	105	1½	11	.021	.....
	A. B.	12/17/07	6+ mos.	3710	3, 6, 1.			8	105	2½	25	.028	.....
	A. B.	12/20/07	6½ mos.	3730	3, 6, 1.			8	105	1½	57	.006	.....
	A. B.	1/5/08	7 mos.	4040	Breast-milk			8	900 to	1	70	.009	Gained 320 gm. in 1 week.
	A. B.	1/12/08	7 mos.	4325	Breast-milk			8	1000	1½	45	.016	Gained 285 gm. in 1 week.
3	A. B.	1/19/08	7 mos.	4505	Breast-milk			8	Daily	2	50	.006	Gained 180 gm. in 1 week.
	C. T.	1/2/08	3½ mos.	2990	3, 6, 1.			8	105	1½	12	.04	.....
	C. T.	1/13/08	4 mos.	3010	3, 6, 1.			8	105	1½	52	.01	.....
	C. T.	1/20/08	4½ mos.	3170	3, 6, 1.			8	105	1¾	12	.03	.....
4	D. K.	1/25/08	4½ mos.	4270	3.5 6.5 1.			8	150	1	55	.002	Fat intolerance; fat crystals in feces; symptoms subsided on whey mixture.
	D. K.	1/27/08	4½ mos.	4250	{ 12 % cream, 240 e.c. Whey..... 720 e.c.			8	120	1½	6	.024	.....
	D. K.	1/29/08	4½ mos.	4230	" "			8	120	2	29	.092	.....
	D. K.	1/31/08	4½ mos.	4250	" "			8	120	1	75	.002	.....
5	D. S.	1/25/08	3 mos.	3940	{ 12 % cream, 210 e.c. Whey..... 630 e.c.			8	105	1¾	43	.003	Gained 410 gm. in 14 days.
6	C. T.	1/27/08	5 mos.	3150	{ 12 % cream, 180 e.c. Whey..... 780 e.c.			8	105	1½	15	.046	.....
	C. T.	1/31/08	5 mos.	3310	" "			8	120	1	42	.02	.....
7	M. F.	1/25/08	3½ mos.	3350	3.5 6.5 1.			8	105	1¼	45	.094	Died Feb. 17 of acute military tuberculosis; chr. glandular tub.
	M. F.	1/29/08	3½ mos.	3250	3.5 6.5 1.			8	105	2¼	30	.006	.....



TABLE 2.—(Continued)

No.	Name.	Date.	Age.	Weight Gm.	Food.	Feed- ings. In 24 Hours.	Quantity c.c. Each Time.	Stomach Contents.			Remarks.
								Ob- tained After Feeding. Hour.	Quantity Ob- tained, c.c.	Chlorin in 100 c.c.	
8	R.....	2/26/08	8 mos.	4275	{ 3.5      7.      1.25 Fat.    Sugar.    teln. { Breast-milk	4	180	1	90	.005	Stomach contents obtained after modified milk feeding; gained 615 gm. in last 11 days.
WELL-NOURISHED INFANTS											
9	J. H.....	1/23/08	18 days	1960	Whey	10	45	1	5	.01	Premature infant. Breast-milk first 15 days.
10	A. C.....	12/20/07	20 days	2420	Whey	10	60	2	10	.048	Remained in hospital 26 days and gained 430 gm. in same food.
	A. C.....	12/28/07	28 days	.....	6.      .75	10	60	1½	17	.026	.....
11	E. G.....	1/7/08	8½ mos.	8000	{ Breast-milk Cow's milk, 120 c.c. { Barley water, 60 c.c. "	5 1 "	180	1½	55	.025	{ Infant had pyelitis and lost weight while in hospital. Stomach contents obtained after breast-milk feedings.
	E. G.....	1/26/08	.....	.....	"	"	180	1	80	.046	.....
12	A.....	2/25/08	7 mos.	8550	{ 3.50    6.50    1.50 { Breast-milk	4 4	210	1½	75	.01	Wet-nurses' baby (normal).
*	A.....	2/26/08	7 mos.	.....	.....	4	.....	1	30	.12	.....
13	M.....	2/26/08	5½ mos.	7290	{ Cow's milk mixture { Breast milk	4 4	.....	1	95	.05	.....
14	F.....	2/26/08	6 mos.	7320	Specimen obtained after breast feeding.	4	.....	1	32	.09	Last 3 wks. supposed to have had cow's milk 8 feedings.
15	D.....	2/26/08	3 mos.	5370	{ Cow's milk mixture { Breast milk	4 4	.....	1	12	.03	Formerly 1 breast and 4 cow's milk. Said to have vomited after last feeding.
16	K.....	2/25/08	3 mos.	7260	Breast milk	..	.....	3½	5	.035	.....
17	G.....	2/25/08	5½ mos.	6000	Breast-milk (?)	..	.....	1	60	.005	Baby fed before coming to hospital; said to be breast-fed.

\* Free hydrochloric acid was tested for by Glinzberg's test in every case. A positive reaction was obtained but once (Case 12)

## DISCUSSION OF DATA

A possible relation of the amount of stomach contents to the degree of acidity could not be determined accurately, but appeared not to be present in this series. In most instances, repeated examinations of the stomach contents obtained from the same atrophic infant from one to two and a half hours after eating showed little, if any, increase in the hydrochloric acid as the result of prolonged digestion.

Cases 2, 5, and 8 show very marked gains in weight with only a trace of hydrochloric acid in the gastric juice. Case 2 is especially interesting. This infant was a typical example of infantile atrophy. Some idea of his emaciation may be gained by comparing his age and weight (6 months old and weighing a little over 8 pounds). He had been under observation for seven and a half weeks and had been fed on modifications of cows' milk during this time. His weight, when first observed, was 3,990 gm. For three weeks he was given 960 gr. a day of a whey-and-cream mixture. He lost weight and did not digest the food well. He was given a modification of milk without any whey for one week without any improvement. He was put back on the cream-and-whey mixture for two weeks, and on and after December 4 he was given 840 c.c. daily of a modification of milk which contained approximately 3 per cent. of fat, 6 per cent. of milk-sugar and 1 per cent. of protein. His weight at this time was 3,860 gm. The hydrochloric acid was determined four times between December 14 and 21, and showed only a trace of acid. He continued to take this food until December 21. On December 21, his weight was 3,730 gm. He was transferred to the Massachusetts Infants Asylum where, through the kindness of Dr. E. C. Stowell, I was able to procure breast-milk for him. On December 29, his weight was 3,720 gm. From December 21 to December 29, he had been fed on a whey-and-cream mixture and very little breast-milk and had not gained in weight. On December 29 and for the following three weeks he was fed on breast-milk alone, of which he took on an average 960 gm. daily. On January 5 he had gained 320 gm.; on January 12, 285 gm.; and on January 19, 180 gm., making a total of 785 gm. in three weeks (approximately  $1\frac{3}{4}$  pounds). We ascribed the diminished gain of the third week to a change in wet-nurses, because during the third week the daily quantity of milk taken was not so large. We were unable to continue the observation any longer, because of the scarcity of breast-milk, and so he was given some breast-milk, but mostly modified cows' milk. The infant responded to the change in the food by ceasing to gain weight. Two months later he had gained only 200 gm.

Three determinations of hydrochloric acid, made at intervals of a week during the three weeks in which the gain in weight was so marked, showed no increase of hydrochloric acid.

Two things are important in this observation: first, the ability to assimilate a suitable food and to gain in weight at once without requiring time for the impaired functions to become restored, the infant previously having proved his inability to digest and gain in weight on certain mixtures of cows' milk in which the percentages of fat, sugar and proteid approximated those of human milk; second, the fact that the infant was able to do this without the aid of much hydrochloric acid. So far as the second point is concerned, if a number of similar observations were found to coincide, it would tend to show that, whatever part the hydrochloric acid may play in producing atrophy, it is not, under certain conditions, essential to recovery.

Patient 5 was under observation for two weeks. During this time he was fed on a whey-and-cream mixture and gained 410 gm. (approximately 14 ounces). One determination of hydrochloric acid was made and only a trace found. This infant was 3 months old and weighed 3,940 gm. (approximately 8 $\frac{3}{4}$  pounds). He did not present so extreme a degree of emaciation as some of the others. This food appeared to be suitable for this infant for the limited time that he was under observation.

Patient 8 was an extremely emaciated infant. He was 8 months old and weighed only 4,275 gm. (approximately 9 $\frac{1}{2}$  pounds). On four feedings each of breast-milk and a modification of cows' milk he gained a little over 20 ounces in eleven days (615 gm.). The only examination that was made of the gastric juice showed a mere trace of hydrochloric acid.

The ability to gain in weight with very little hydrochloric acid in the gastric juice may throw light on the two cases which I reported last year (see Table 1, Cases O and P). Both of these infants had been atrophic, but had made marked gains in weight during the six or eight weeks preceding the time that the gastric contents were obtained. A single determination of hydrochloric acid made in each case showed it to be very much diminished.

#### SUMMARY OF RESULTS

1. The Sjöquist method rarely showed more than a trace of hydrochloric acid in the stomach contents from atrophic infants fed on cows' milk mixtures.

2. Out of twenty-one determinations made of hydrochloric acid in the stomach contents obtained from eight infants, ten showed a percentage of hydrochloric acid between 0.01 and 0.05, and eleven showed a percentage of hydrochloric acid between 0.002 and 0.009. These results correspond fairly well with eight determinations made last year (see Table 1) on the stomach contents from eight atrophic infants of which seven showed percentages of hydrochloric acid between 0.01 and 0.041; and one showed a percentage of 0.07 hydrochloric acid.

The stomach contents from nine well-nourished infants showed a diminished amount of hydrochloric acid. The diminution of hydrochloric acid corresponded closely to that found in about one-half of the determinations made on the above-mentioned atrophic infants. Out of twelve determinations of hydrochloric acid in the stomach contents obtained from nine infants, one showed 0.12 per cent., one showed 0.09 per cent., nine showed percentages between 0.01 and 0.05; and one showed 0.005 per cent. hydrochloric acid. Thus the diminution of hydrochloric acid, although it was marked, was never so extreme as in one-half of the determinations obtained from atrophic infants. Repeated examinations could not be made in the normal cases and so the constancy of these results is problematical.

These results do not correspond well with those obtained last year from well-nourished infants (see Table 1) in which the percentages of hydrochloric acid were much higher.

3. From this series of observations it is not possible to show any definite or constant relation between the quantity of stomach contents obtained and the percentage of hydrochloric acid present. This statement applies equally well to any relations that may exist between the character of the food and the production of hydrochloric acid.

4. Examinations of the stomach contents obtained from the same atrophic infants at different periods of time after eating, and without any change in the diet, rarely showed any marked variations in the quantity of hydrochloric acid present.

5. The results of these observations do not prove that a marked diminution of hydrochloric acid in the gastric juice is an essential factor in the production of infantile atrophy, although they do show that this diminution is constant. On the other hand, considerable evidence is afforded by several of the observations that it is possible for atrophic infants to gain very rapidly in weight and yet produce very little hydrochloric acid in the gastric juice. This appears to show that the quantity

of hydrochloric acid in the gastric juice is not an important factor in recovery from infantile atrophy.

Briefly, then, these observations show the following facts:

1. A constant and marked diminution of hydrochloric acid in the gastric contents from atrophic infants.
2. Great variations in the quantity of hydrochloric acid in the gastric contents from well-nourished infants.
3. In this series of cases of infantile atrophy, there was little, if any, increase of hydrochloric acid in the gastric juice as the result of prolonged digestion.

A few words in conclusion about the method employed in these observations. These observations were not made for the purpose of comparing normal and atrophic infants, nor was it intended to show the exact quantity of hydrochloric acid present in the gastric juice from atrophic infants. The sole purpose was to find out whether hydrochloric acid was constantly and markedly diminished in the gastric juice in cases of infantile atrophy. Any criticism that may be made as to the accuracy of the Sjöquist method when milk is the diet is irrelevant when applied to my results, because only such a constant and marked difference between the normal and the atrophic infant as to place the result beyond the range of error in the method could be of value so far as my hypothesis was concerned.

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## THE EFFECT OF TREATMENT ON THE WASSERMANN REACTION\*

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The diagnostic value of the Wassermann reaction, now well recognized, has, as a direct corollary, the importance of the test as a guide to treatment.

In much of the earlier work it was found that the frequency of negative reactions, especially in the latent stage, bore a direct relation to the amount and efficiency of previous treatment. Later statistics have confirmed the early observations, and to-day it is recognized that the value of a negative reaction, from a diagnostic standpoint, is much affected by recent specific medication.

The view one takes of a positive reaction in the latent stage has much to do with his opinion in regard to the reaction as a guide to treatment. Two possibilities exist: A positive reaction may indicate (1) that the patient once had syphilis and his serum still shows evidence of the old infection, and (2) that spirochetes are present somewhere in the body or, in other words, that an active syphilis exists without manifestations. A few hold to the first possibility, but the majority of investigators maintain that a positive reaction means active syphilis. Among those who present this view most emphatically are Neisser, Bruck, Citron, and Lesser.

From a theoretical standpoint Citron<sup>1</sup> advances the following arguments in favor of the view that a positive reaction means active syphilis:

1. The constant findings of the reaction in manifest syphilis.
2. The fact that untreated or poorly treated individuals show the reaction after ten years or more, whereas in other diseases bacterial antibodies diminish or disappear a few months after the disease has ceased to be active. If the syphilis reaction is present after ten years, it must be due to the constant production of an antibody brought about by the presence of the spirochete.
3. The further fact that in latent cases with a primary positive Wassermann reaction, the reaction may disappear under treatment, indicating

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\* From the Department of Pathology, The University and Bellevue Hospital Medical College. Aided by a grant from the Committee on Scientific Investigation of the American Medical Association.

1. Citron, J., *Handbuch der Immunitätsforschung*, 1909, ii, 1111.

that, as a result of specific therapy, toxic substances are removed, the formation of the antibody ceases, and the reaction gradually becomes weaker, or entirely disappears.

Baisch,<sup>2</sup> in his study of Colles' law, by the use of the Wassermann reaction found that, in women bearing syphilitic children and giving a positive reaction, spirochetes could be demonstrated in the maternal portion of the placenta. He considers the reaction, therefore, to be always an indication of the presence of active spirochetes. Thus, from both indirect and direct evidence we must conclude that a positive reaction means the presence of living spirochetes, although the converse is not necessarily true.

In the study here presented of the relation of treatment to the frequency of positive reactions in latent syphilis, I have divided the cases into two groups, representing the early and late stages, respectively. In the first group are placed those cases which present a history of three years or less since infection; and in the second, all with a longer history (Table 1). The time of treatment is given in months and years, because in this country the chronic intermittent treatment is not followed so extensively as in Germany.

TABLE 1.—EFFECT OF TREATMENT ON LATENT SYPHILIS

EARLY LATENT			
Amount of Treatment.	No. Cases.	No. Positive.	% Positive.
None .....	10	9	90
6 months .....	31	26	87
1 year .....	19	13	70
18 months .....	5	3	60
2 years .....	9	5	55
LATE LATENT			
None .....	2	2	100
6 months .....	22	13	60
1 year .....	17	8	47
18 months .....	6	4	66
2 years .....	22	13	60
30 months .....	5	3	60
3 years .....	40	16	40
4 years .....	12	4	33
5 years .....	4	1	25
6 years .....	3	1	33

It will be noted that in the early period of latent syphilis the percentage of positive reactions falls in proportion to the amount of treatment. This is no doubt due to the fact that, in this stage, the patients are more directly under the influence of the mercury than they are at a

2. Baisch, K.: München. med. Wehnschr., 1909, lvi, 1929.

later period. In the late period the percentage of negative reactions is nearly as high in those patients who have had six months' treatment as in those who have had thirty months' treatment, but the curve falls rather sharply in the cases treated three years or more. One might argue from such figures that six months' treatment is as efficient as one of two and one-half years. Indeed, Lesser<sup>3</sup> concludes that four courses of treatment represent the maximum of efficiency, because in late latent stages he obtained 54 per cent. negative reactions in patients who had undergone four courses, and only 53 per cent. negative reactions in those who had taken six courses. It seems to me, however, that this point is not well taken, unless it can also be demonstrated that the remaining positive reactions fail to become negative under continued energetic treatment.

In this regard the results of Jesionek and Meirowsky<sup>4</sup> are of interest. They found a steady fall in percentage of positive reactions during eight courses of treatment; thus, the percentage of positive reactions in patients who had undergone four and five courses was 42, and this fell to 31 in those who had eight or more courses.

In the study of tabes also the amount of treatment seems to bear a definite relation to the disappearance of a positive reaction, as is seen in Table 2. On the other hand, this table does not indicate the incidence of tabes in individuals with negative and positive reactions, respectively. The solution of this problem will come only after the lapse of time and the study of large groups of cases. Incidentally, the number of negative reactions in untreated and little-treated cases indicates the number of cases, 25 per cent., in which, according to practically all observers, a negative reaction is to be expected in this disease.

TABLE 2.—TREATMENT IN TABES

	No. Cases.	No. Positive.	% Positive.
Untreated .....	24	18	75
Little treated .....	12	9	75
Fairly well treated.....	15	8	53
Well treated .....	8	3	37

The effect of specific therapy on the reaction is, however, most clearly demonstrated in those investigations in which patients under treatment have been tested repeatedly. Table 3 shows the collected statistics of thirteen workers who have studied this question.

3. Lesser, F.: *Deutsch. med. Wchnschr.*, 1910, xxxvi, 116.

4. Jesionek and Meirowsky: *München. med. Wchnschr.*, 1909, lvi, 2297.



TABLE 3.—EFFECT OF TREATMENT (FROM LITERATURE)

Author.	Stage.	No. Cases.	Became Negative.	Weaker.	Unaltered.	Stronger.	Remarks.
Mueller <sup>5</sup> .....	I.....	3	0	1	1	1	.....
Fischer <sup>6</sup> .....	I.....	17	9	4	..	2	Two originally negative remained negative.
Reinhart <sup>7</sup> .....	I.....	56	45	..	..	11	.....
		Negative.	Remained negative.			Became positive.	
Reinhart <sup>7</sup> .....	I.....	48	16	..	32	..	.....
		Positive.					
Mueller <sup>5</sup> .....	II early.....	24	1	9	14	..	.....
Fischer <sup>6</sup> .....	II early.....	13	9	3	1	..	.....
Boas <sup>8</sup> .....	II early.....	82	76	..	6	..	.....
Pürckhauer <sup>9</sup> .....	I and II.....	116	75	..	41	..	.....
Lesser <sup>10</sup> .....	II.....	17	10	4	2	..	.....
Blaschko <sup>11</sup> .....	Early with symptoms.	41	36	..	5	..	.....
Mueller <sup>5</sup> .....	II relapsing.....	15	1	7	7	..	.....
Fischer <sup>6</sup> .....	II relapsing.....	28	0	10	14	4	.....
Reinhart <sup>7</sup> .....	II.....	Not stated.	45%	30%	25%	..	.....
Mueller <sup>5</sup> .....	III.....	7	0	1	6	..	.....
Fischer <sup>6</sup> .....	III.....	17	4	4	5	4	.....
Lesser <sup>10</sup> .....	III.....	1	..	1	..	..	.....
Blaschko <sup>11</sup> .....	Late with symptoms.	11	9	..	2	..	.....
Pürckhauer <sup>9</sup> .....	III.....	18	2	..	16	..	.....
Pürckhauer <sup>9</sup> .....	Cerebral.....	4	1	..	3	..	.....
Citron <sup>12</sup> .....	With symptoms.	23	15	12	5	1	.....
Blaschko <sup>11</sup> .....	Latent early.....	23	18	..	5	..	.....
Pürckhauer <sup>9</sup> .....	Latent early.....	12	4	..	8	..	.....
Blaschko <sup>11</sup> .....	Latent late.....	15	13	..	2	..	.....
Pürckhauer <sup>9</sup> .....	Latent late.....	15	4	..	11	..	.....
Fischer <sup>6</sup> .....	Latent.....	12	5	4	2	..	One negative became positive.
Lesser <sup>10</sup> .....	Latent.....	6	3	1	2	..	.....
Citron <sup>12</sup> .....	Latent.....	25	12	5	6	2	.....
Heller <sup>13</sup> .....	Not stated.....	57	22	17	18	..	.....
Hoehne <sup>14</sup> .....	Not stated.....	211	92	25	94	..	.....
Schönnefeld <sup>15</sup> .....	Not stated.....	10	5	1	7	..	.....
Alt <sup>16</sup> .....	General paralysis.	31	7	..	26	..	Treated with arsenophenylglycin.
Alt <sup>16</sup> .....	Epilepsy.....	6	4	..	2	..	Treated with arsenophenylglycin.

5. Müller, R.: Wien. klin. Wchnschr., 1908, xxi, 282.

6. Fischer, W.: Arch. f. Dermat. u. Syph., 1910, c, 215.

7. Reinhart, A.: München. med. Wchnschr., 1909, lvi, 2092.

8. Boas, H.: Berl. klin. Wchnschr., 1909, xvi, 400, 588.

9. Pürckhauer, R.: München. med. Wchnschr., 1909, lvi, 698.

10. Lesser, F.: Deutsch. med. Wchnschr., 1909, xxxv, 379.

11. Blaschko: Deutsch. med. Wchnschr., 1909, xxxv, 383.

12. Citron, J.: Med. Klin., 1909, v, 86.

13. Heller, F.: Inang. Diss., Gießen, 1908.

14. Hoehne, F.: Berl. klin. Wchnschr., 1909, xvi, 869.

15. Schönnefeld: Inang. Diss., Bonn (cited by Bruck, Die Serodiagnose der Syphilis, p. 1021).

16. Alt, K.: München. med. Wchnschr., 1909, lvi, 1457.

TABLE 4.—INFLUENCE OF TREATMENT ON SUCCESSIVE REACTIONS \*

No. and Stage.	Time Since Infection.	Amount of Treatment to Time of First Reaction.	First Reaction	Treatment.	Second Reaction.	Treatment.	Third Reaction.	Remarks.
1 I.	.....	None	++	30 inj. Hg bin iodid	++ (N++)	40 inj. biniodid.	++ (N+)	No secondaries.
2 I.	.....	None	++	4 mos. pill bichlorid	++	30 innuements.	++	24 innuements; 4th reaction ++; secondaries resistant to treatment.
3 I.	3 wks.	None	+-	2 inj. Hg salicylate.	++	.....	.....	No secondaries.
4 I.	2 wks.	None	.....	No treatment, 6 wks. later.	++ (N++)	8 inj. Hg salicylate.	++ (N+)	No secondaries.
5 I.	3 wks.	None	++ (N++)	24 inj. Hg biniodid.	(N+)	.....	.....	No secondaries.
6 II. Early	.....	None	++	18 inj. Hg salicylate.	+	.....	.....	No secondaries.
7 II. Early	4 wks.	None	++	14 inj. Hg salicylate.	(N-)	.....	+	Relapse 2 wks. later.
8 II. Early	3 mos.	None	++	6 wks. pill bichlorid. Rest 6 weeks.	++	.....	.....	.....
9 II. Early	5 wks.	None	++	30 inj. Hg biniodid.	++ (N++)	40 inj. Hg biniodid; rest 3 mos.	++ (N+)	.....
10 II. Early	3 mos.	None	++	3 mos. pill bichlorid.	++	.....	.....	.....
11 II. Early	.....	None	++	18 innuements.	++	.....	.....	.....
12 II. Early	.....	None	++	4 mos. pill bichlorid.	++	35 innuements.	++	.....
13 II. Early	6 wks.	3 wks. pill protoiodid	++	12 wks. pill protoiodid	+-	.....	.....	Easily mercurialized.
14 II. Early	.....	.....	++	36 innuements; 6 wks. mixed.	++	.....	.....	.....
15 II. Early	2 mos.	12 inj. Hg biniodid.	+	24 inj. Hg biniodid; 2 mos. pill protoiodid.	++ (N++)	.....	.....	.....
16 II. Early	.....	None	++	24 innuements.	++ (N++)	.....	.....	.....
17 II. Early	2 mos.	3 inj. Hg salicylate.	++	7 inj. Hg salicylate.	++ (N++)	4 inj. Hg salicylate.	++ (N++)	{ 3 inj. Hg salicylate, ..... } Fourth Reaction (N+)           { 7 inj. Hg salicylate, ..... } Fifth Reaction (N+)           { 2 inj. Hg salicylate, ..... } Sixth Reaction (N+)           { rest 2 mos. }

\* N Indicates Nozuehl method.

18	II. Early.....	None	+	2 mos. pill protothid.....	1 (N +)	
19	II. Relapsing. 8 mos. 2 mos. pills.....	+	42 injections.....	+	18 injections; 8 wks. mixed.	++
20	II. Relapsing. 2 yrs. "Little".....	+	15 inj. Hg bichlorid; 2 mos. pill protothid.....	+		
21	II. Relapsing. 6 mos. 7 inj. Hg salicylate.....	+	5 mos. mixed; 2 mos. Jones mixed.....	(N++)		
22	II. Relapsing. 9 mos. 8 wks. pills; 12 injections.....	+	4 mos. mixed.....	(N++)	6 wks. mixed	(N++)
23	II. Relapsing. 10 mos. 27 inj. Hg bichlorid.....	+	4 mos. mixed.....	(N++)		
24	II. Relapsing. ? ? .....	+	5 mos. mixed.....	++		
24A	III.....	+	18 inj. Hg salicylate.....	(N++)		
25	III.....	(N)	5 wks. mixed.....	(N++)	4 wks. pill bichlorid; 4 wks. mixed.	(N++)
26	III.....	+	66 injection.....	+	6 wks. pill bichlorid	1 mos. later without treatment: Reaction
27	III.....	+	57 inj. Hg salicylate.....	++		Malignant syphilis; very resistant to treatment.
28	III.....	++	18 inj. Hg salicylate.....	++		
29	III.....	+	2 mos. mixed.....	+		
30	III.....	+	35 fumigations.....	++	31 fumigation	
31	III.....	+	2 mos. mixed.....	++		
32	III.....	+	12 wks. mixed; 12 wks. Jones mixed.....	+		
33	III.....	+	30 injection; K1 gr. 40 a day; 1 mo. mixed.....	++		
34	III.....	+	15 injections; 4 inj. Hg salicylate; 4 mos. Jones mixed.....	+		
35	III.....	+	21 wks. mixed; none for 6 weeks.....		None for 2 mo	
36	III.....	+	16 inj. Hg salicylate; none for 1 month.....	(N)		

TABLE 4.—INFLUENCE OF TREATMENT ON SUCCESSIVE REACTIONS—Continued

No. and Stage.	Time Since Infection.	Amount of Treatment to Time of First Reaction.	First Reaction.	Treatment.	Second Reaction.	Treatment.	Third Reaction.	Remarks.
37 III.	5 yrs.	None	++	9 mos. mixed	+	3 mos. pill bichlorid	++	Relapse 2 wks. after last reaction.
38 III.	?	None	++	4 wks. mixed; 6 wks. Jones mixed.	+			
39 III.	?	None	++	2 mos. mixed; none for 10 mos.	+			
40 III.	3 yrs.	5 mos.	++	7 wks. mixed; none for 5 mos. (Relapse.)	++			
41 III.	8 yrs.	6 mos. pills.	++	19 inj. Hg salicylate	+	7 inj. Hg salicylate	+-	
42 III.	4 yrs.	Irregular	+	28 injections; 9 inj. Hg salicylate; 3 mos. KI.	++	12 inj. Hg salicylate; 1 mo. mixed; none for 6 mos.	+-	
43 III.	3 yrs.	None	+	3 mos. mixed	+- (N +)	7 wks. mixed	+- (N +)	
44 III.	9 yrs.	None	++	10 wks. mixed	++			
45 III.	?	5 wks. mixed	+	None for 5 mos.	++			
46 III.	?	None	++	5 mos. mixed	+-			
47 III.	?	Little	+	3 mos. mixed	+- (N + -)			
48 III.	7 yrs.	60 insol. inj.; 20 solub. inj.	+-	17 inj. bichlorid; KI till 1 mo. ago.	+	6 inj. bichlorid; 4 wks. mixed.	+	
49 III.	3 yrs.	2½ yrs. injections and pills.	+-	30 injections; none for 1 mo.	+	7 mos. pill bichlorid	-	Reaction remained negative for 6 mos., then became +- (N +).
50 III.	14 yrs.	3 mos.	++	6 mos. mixed	++			
50A Latent (early)	3 mos.	6 inj. Hg salicylate	+-	4 mos. mixed	+	13 inj. Hg salicylate; 5 mos. mixed.	+	2 mos. Jones mixed; 4th reaction ++. Takes treatment poorly.
51 Latent (early)	15 mos	15 inj. Hg salicylate; 1 yr. pills.	+-	4 mos. pill protiodid	+-	8 wks. mixed; 6 inj. Hg salicylate.	+-	

52	Latent (early)...	16 mos.	12 inj. Hg salicylate; 50 immuncions; 600 protoid pills.	(N-)	Rest 10 wks.	+	(N++)	20 immuncions; rest 1 mo.	(N-)	Rest 6 wks.; 4th reaction +-(N+).
53	Latent (early)...	2 yrs.	2 yrs. injections and pills.	-	1 mo. rest.		+			Relapse.
54	Latent (early)...	10 mos.	100 immuncions; none for 1 mo.	++	6 immuncions; 3 mos. pill bichlorid.		+			
55	Latent (early)...	18 mos.	17 mos. pills.	+	3 mos. mixed.		+-	5 mos. mixed.	+	
56	Latent (early)...	18 mos.	6 mos.	+(N++)	3 mos. mixed; none for 8 mos.		(N-)			
57	Latent (early)...	2 yrs.	2 yrs. pills.	+	3 mos. mixed.					Reaction taken every 2 mos. for 8 mos.; all negative.
58	Latent (early)...	4 yr	1 yr.	(N-)	2 mos. rest.		++(N++)			Cerebral symptoms 2 wks. later.
59	Latent (early)...	5 mos.	10 wks. pills.	+	3 mos. pill bichlorid.		+	3 mos. pill bichlorid; 1 mo. mixed.	+-	
60	Latent (late)...	4 yrs.	3 yrs. mixed.		Rest 2 mos.		(N-)	Rest 7 wks.	(N+)	
61	Latent (late)...	3 1/2 yrs.	3 yrs. injections and mixed.	+	13 inj. bichlorid.			None for 6 mos.		
62	Latent (late)...	3 yrs.	3 yrs. pill protoidid.	+(N+)	30 immuncions.		-(N+)	20 immuncions; rest 3 wks.	(N-)	
63	Latent (late)...	8 yrs.	90 immuncions; 12 inj. Hg salicylate; 2 yrs. mixed.	++	80 immuncions.		+(N++)	30 immuncions.	-(N++)	
64	Latent (late)...	8 yrs.	3 yrs.	+	11 wks. mixed.					Reactions taken every 2 mos. for 1 yr.; all negative.
65	Latent (late)...	22 yrs.	1 yr.	++	2 mos. mixed.		++	4 mos. mixed; none for 2 mos.		
66	Latent (late)...	5 yrs.	2 1/2 yrs. pills.	+	Irregular; mixed and immuncions 5 mos.		+			
67	Congenital	?	60 immuncions.	(N++)	150 immuncions.		(N+)			
68	Tubes	9 yrs.	Irregular.	+	6 mos. mixed treatment.		+	45 inj. bichlorid.	-	Rest 6 mos.; 4th reaction -

Special reference must be made to some of these figures. It will be noted that the reaction is more readily influenced in the primary stage than later in the disease. Many of Reinhart's cases of primary syphilis were treated with arsacetin; of 35 negative reactions in this stage, 13 became positive and 22 remained negative; while of 48 positive reactions, 32 remained positive and 16 became negative. In Alt's cases also the influence of arsenophenylglycin on the reaction is evident. The arsenic preparations are thus shown to have a distinct place among antisyphilitic remedies.

Among Boas' 16 patients in the early secondary stage, in all of whom the reaction became negative under one course of inunctions, only three showed a clinical relapse within a month; while of the six patients with a persistent positive reaction five had a relapse in the same period. Later in the disease, all individuals with latent syphilis and a positive reaction who were not treated presented active symptoms, while all those who gave a positive reaction and were treated remained free from symptoms.

The influence of specific therapy in latent syphilis is well illustrated by Hoehne's<sup>14</sup> study of prostitutes. Among twenty-three *puella publica* who gave a positive reaction but denied any syphilitic history, fourteen were energetically treated; in seven of these the reaction became absolutely negative and in two others it was weaker. Practically all observers agree on two points: (1), that the reaction more readily becomes negative under treatment in the early stages of the disease than it does in the late stages; and (2), that in the early stage a serum reacting negatively is more liable to become positive when treatment is intermitted than is the case in the late stages.

In Table 4 is presented the influence of treatment in cases which I have followed during the past two years. The Wassermann reaction was used throughout the series, and in a majority of tests the Noguchi modification was also applied. When the results of both methods were the same they are recorded as one examination; but when the results of the two methods differed, both reactions are noted.

A summary of Table 4, showing the total change in the Wassermann reaction in the cases under treatment, not including periods of intermissions from treatment, is given in Table 5

TABLE 5.—SUMMARY OF TABLE 4

Stage.	Cases. No.	Negative.		Weaker.		Unaltered.		Stronger.	
		No.	Per ct.	No.	Per ct.	No.	Per ct.	No.	Per ct.
I .....	5	1	20	2	40	1	20	1	20
II Early .....	13	1	8	7	54	5	38	..	..
II Relapsing .....	6	1	17	3	50	2	33	..	..
III .....	26	5	19	10	39	9	35	2	7
Latent early .....	8	3	38	3	38	1	17	1	17
Latent late .....	7	3	42	2	29	2	29	..	..

Although it would appear that treatment has as great an effect in producing negative reactions in the late as in the early stages, it will be noted that most of the reactions which became negative in the late period were only partially positive at the time of the first reaction. These patients had previously received much treatment, which fact must be taken into consideration in order to estimate properly the results of treatment. Strongly positive reactions in either the tertiary or late latent periods are much harder to influence than similar reactions in the early periods, while the maximum of influence seems to be in the primary stage. This would speak most strongly for the early energetic treatment of syphilis. Of special interest on this point are the figures of Merz,<sup>17</sup> who analyzed the cases tested in Neisser's clinic. In all stages, those patients who had been treated early in the primary stage gave about half as many positive reactions as those patients who had not been treated until after the secondary symptoms had appeared. With the newer methods of diagnosis at our disposal, the early treatment can be given with more assurance that we are treating syphilis, and not simply chancreoid, and with a better prognosis than if treatment is delayed until general secondary symptoms appear. Among my five cases in the primary stage, four were treated by injections and showed no further symptoms. The fifth patient at first refused any form of treatment except pills. As a result, resistant secondary symptoms appeared and later, when he consented to undergo inunctions, the reaction was much harder to influence.

It will be noted that the Noguchi reaction, in which active serum was used, was stronger and persisted much longer under treatment than did the Wassermann method with inactive serum. Boas also noted the fact that active serum gives a more persistent reaction under treatment than does inactive serum, but we have otherwise no definite comparison of the two methods under the influence of treatment. If, therefore, we regard a positive reaction with active serum as a proper guide to treatment, the percentage of positive reactions will be greater, and the periods of intermission from treatment will necessarily not be as numerous as they have been with the use of the Wassermann reaction alone. As a rule, a serum which shows a weakly positive Wassermann will give a positive or strongly positive Noguchi reaction, so that we must regard a weakly positive Wassermann reaction as an indication for further medication.

In the few cases in which treatment was stopped because of a negative reaction, the positive reaction appeared again in a shorter time in the cases in the early stages than in those in the later stages.

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17. Merz, H.: Cited by Bruck. *Die Serodiagnose der Syphilis*, p. 116.

The effect of the different modes of administration of mercury has been studied by various observers with but little unanimity as to the best form. Blaschko<sup>11</sup> states that in his experience no preference can be given to either inunction or injection. Pürekhauser<sup>9</sup> favors the "insoluble injections." Boas<sup>8</sup> obtained an extraordinarily high percentage of negative reactions after one course of inunctions. Hoehne<sup>14</sup> noted a change in the reaction in about 70 per cent. of individuals receiving injections of either salicylate of mercury or the soluble salts. The most marked influence, however, was obtained from the injection of calomel, which caused 83 per cent. of the reactions to become weaker. Only 33 per cent. of his cases treated by inunctions showed any diminution in intensity.

In the cases of latent syphilis in which I did but a single test, I have noted the relation of negative reactions to the kind of treatment the patient had received. In the early latent stage, negative reactions were obtained in 24 per cent. of those patients who had taken treatment only by mouth; in 23 per cent. of those who had received internal treatment combined with injections or inunctions; and in 50 per cent. of those who had received injections only. In the late latent stage, patients receiving pills or mixed treatment gave 54 per cent. of negative reactions; those receiving combined treatment, 60 per cent.; and those treated by injections alone, 83 per cent. The relative efficiency of the different forms of treatment is better illustrated in those patients in whom repeated tests were made (Table 6).

TABLE 6.—ILLUSTRATING INFLUENCE OF FORM OF TREATMENT

No. cases	Injections Bichlorid.	Injections Biniodid.	Injections Salicylate.	Inunctions.	Pill Bi- chlorid.	Mixed Treatment.
	3	7	14	17	10	28
Negative	66%	30%	21%	18%	20%	14%
Weaker	..	70%	50%	24%	20%	40%
Unaltered	..	..	21%	58%	50%	32%
Stronger	33%	..	8%	..	10%	14%

The superiority of injections over the other forms of treatment is well illustrated by this table. Mercuric iodid seems to have given the best results. The apparent inferiority of the inunction method may be explained by the fact that dispensary patients do not apply inunctions properly. In private patients who used this form of treatment properly, as marked an effect was obtained as in any other form of treatment. The tendency of the reaction to become stronger during treatment was most marked in those patients receiving internal treatment. It is of interest, also, that in three patients in whom the intensity of the reaction increased during treatment, a clinical relapse shortly appeared. This observation



impresses one with the importance of adopting a form of treatment which will have the most marked effect on the reaction.

This study has not extended over a sufficient length of time to enable one to form final conclusions. It demonstrates, however, a parallelism between the clinical symptoms, the efficiency of treatment and the intensity of the reaction and indicates most strongly, therefore, the value of the reaction as a guide to treatment. It would appear advisable to drop the old rules concerning treatment and to be guided more largely by the reaction. In this way many patients in the early stages of syphilis may be spared a certain amount of unnecessary medication, and many others in the later stages by continued treatment may possibly be saved from serious visceral manifestations of the disease.

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## THE NORMAL PERCENTAGES OF THE DIFFERENT VARIETIES OF LEUKOCYTES IN INFANTS AND CHILDREN

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A series of differential blood-counts made on apparently normal infants and children serves as the basis of this communication. The investigation was undertaken primarily to determine, if possible, the normal percentages of the cells with eosinophilic granules. In the normal adult these cells are supposed to constitute from 1 to 4 per cent. of the total leukocytes. It is generally stated that in infants and children the normal percentages of the eosinophil leukocytes may be much greater than in adults. Emerson<sup>1</sup> speaks of a physiological eosinophilia of childhood. Wood<sup>2</sup> gives the variations of the eosinophil cells in the nursing period from 1.5 to 0.5 per cent. and in childhood as from 0.7 to 12.5 per cent. Ewing<sup>3</sup> considers the average of the eosinophil cells in childhood 1 to 2 per cent. greater than in adults. The same figures are given by Wile.<sup>4</sup> In institutional children from 1 to 8 years of age, Mosenthal<sup>5</sup> found the average percentage of the eosinophil cells below 5, with the exception of children from 5 to 6 years of age, in whom the percentage was 5.8. According to Bezançon and Labbé<sup>6</sup> the eosinophil cells may be as great as 7 per cent. in children between 5 and 10 years of age. Sahli<sup>7</sup> states that the number of eosinophil leukocytes may be high in normal children.

A wide fluctuation in the percentages of the eosinophil cells in infancy and childhood is shown by the investigations of Müller and Rieder,<sup>8</sup> Cannon,<sup>9</sup> Zappert,<sup>10</sup> Hoek and Schlesinger,<sup>11</sup> Carstanjen<sup>12</sup> and

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1. Emerson: Clinical Diagnosis, J. B. Lippincott Co., Philadelphia, 1906, p. 500.

2. Wood, F. C.: Chemical and Microscopical Diagnosis, 1909, p. 110.

3. Ewing: Clinical Pathology of the Blood, Lea and Febiger, Philadelphia, 1903, p. 137.

4. Wile: New York State Jour. Med., 1910, x, 205.

5. Mosenthal: Arch. Pediat., 1908, xxv, 831.

6. Bezançon and Labbé: Traité d'Hématologie, Paris, 1904, p. 497.

7. Sahli: Lehrbuch der klinische Untersuchungs-Methoden, Leipzig, 1902.

8. Müller and Rieder: Deutsch. Arch. f. klin. Med., 1891, xlviii, 96.

9. Cannon, Deutsch. med. Wchnschr., 1892, xviii, p. 206.

10. Zappert: Ztschr. f. klin. Med., 1893, xxiii, 227.

11. Hoek and Schlesinger: Beitr. z. Kinderh., 1892, ii, 1.

12. Carstanjen: Jahrb. f. Kinderh., 1900, lii, 215, 233, 684.

Barach.<sup>13</sup> The determinations of Zappert are of especial interest on account of the high percentages of the eosinophil cells found in some of the cases. The eosinophil cells were over 6 per cent. in eighteen of thirty-three individuals from 9 days to 12 years of age; in six instances the percentage was greater than 10. From these investigations Zappert concluded that there was a physiological eosinophilia in individuals under 14 years of age. Few of the children, however, were normal and a number suffered from skin diseases which may be associated with eosinophilia.

The most complete investigations that I have been able to find are those of Carstanjen. Differential blood-counts were made on infants, children and adults, and five determinations were made for each year of life. All cases of acute illness were excluded and the counts were not made on persons with less than 50 per cent. of hemoglobin (Fleischl). A number of the children suffered from chronic diseases or malformations, but the conditions enumerated were in no instance those which are recognized as a cause of eosinophilia. For purposes of comparison, the maximum, minimum and average percentages of the eosinophil cells in individuals between one month and 12 years of age are given in Table 1.

TABLE 1.—MAXIMUM, MINIMUM AND AVERAGE PERCENTAGES IN CHILDREN BETWEEN 1 MONTH AND 12 YEARS

	1-6 mo.	1-2 yr.	3-4 yr.	5-6 yr.	7-8 yr.	9-10 yr.	11-12 yr.
Max. ....	9.35	8.75	9.95	9.1	7.45	9.9	5.15
Min. ....	0.35	0.5	1.9	1.65	1.83	3.15	0.1
Aver. ....	3.59	3.04	5.74	6.22	3.69	5.53	3.10
	6-12 mo.	2-3 yr.	4-5 yr.	6-7 yr.	8-9 yr.	10-11 yr.	
Max. ....	2.85	6.2	16.65	5.05	8.35	16.3	
Min. ....	0.00	0.9	0.75	1.4	2.1	3.6	
Aver. ....	0.76	3.9	6.3	3.34	5.53	7.31	

These investigations, as pointed out by Cabot,<sup>14</sup> do not show that the eosinophil cells are uniformly high in infants and children, but merely indicate that these cells are subject to remarkable oscillation.

The determinations of Barach<sup>13</sup> have the same significance. In 29 differential blood-counts on normal children from 1½ to 7 years of age, the eosinophil cells fluctuated from 0.0 to 13 per cent. In four cases the percentage was greater than 6.

13. Barach, J. H.: Morphology of the Blood in Pertussis. *THE ARCHIVES INT. MED.*, 1908, i, 602.

14. Cabot: A Guide to the Clinical Examination of the Blood. W. Wood & Co., New York, 1904, p. 168.

To determine the normal percentages of the eosinophil cells, it is obviously necessary to exclude all diseases or conditions in which these cells have been found to be increased. The observations of Rosenstern<sup>15</sup> offer an explanation for some of the high percentages of the eosinophil cells found in infants and children. He found that the eosinophilia which may occur in connection with eczema and certain other diseases of the "exudative diathesis" of Czerny may remain after the disappearance of the objective disease. He also found high percentages of the eosinophil cells in dyspeptic infants free from other diseases. In none of six normal breast-fed infants were the eosinophil cells above 3 per cent. In six artificially fed infants the percentages of the eosinophil cells varied from 0.7 to 4.

Peter<sup>16</sup> found the eosinophil cells from 0.9 to 4.62 per cent. in twenty well children. In isolated investigations on new-born infants and numerous investigations on sick and well children, Wolf<sup>17</sup> found the percentages of the eosinophil cells no greater than those normal for adults.

Among the conditions which are often associated with a considerable degree of eosinophilia, and which must be excluded in determining normal percentages, is the presence of intestinal worms. In many instances the common intestinal worms do not give rise to definite symptoms and for this reason it is necessary to examine the stools for the parasites or their ova. Judging by the published reports, this precaution was not taken in the cited investigations which showed high percentages of the eosinophil cells. Boycott<sup>18</sup> found the eosinophil cells below 5 per cent. in eight out of ten normal and "apparently wormless" children. In one case the eosinophil cells were 5.2 per cent.; in another, 5.4 per cent. In another communication<sup>19</sup> I reported blood-counts on twenty apparently normal children who were free from intestinal worms, judging from a negative examination of the stools. In no instance were the eosinophil cells over 6 per cent.; in one case they were 6 per cent. and in another, 5 per cent.

In the present investigation the blood of eighty infants and children between 3 days and 12 years of age was examined. Most of the children were from the poorer classes, but all cases of manifest illness were excluded. Cases were also excluded in which there was a history of any disease recognized as a cause of eosinophilia. The following precautions were taken in the attempt to eliminate helminthiasis: The counts on

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15. Rosenstern: *Jahrb. f. Kinderh.*, 1909, lxi, 631.

16. Peter: *Dermat. Ztschr.*, 1897, iv, 669.

17. Wolf: *Beitr. z. path. Anat. u. z. allg. Path.*, 1900, xxviii, 150.

18. Boycott: *Brit. Med. Jour.*, 1903, ii, 1267.

19. Schloss: *Am. Jour. Med. Sc.*, 1910, cxxxix, 675.

children between 1 and 12 years of age were made only in instances in which the history and a previous examination of the feces was negative. In infants under 1 year of age the feces were examined in cases showing more than 5 per cent. of eosinophil cells.

Before giving the results of the blood-counts a short description of the technic is advisable. The blood-smears were made on new slides, which had been washed in green soap and water, treated with nitric acid, washed half an hour in running water and then placed in 95 per cent. alcohol until used. A small drop of blood obtained from the lobe of the ear without pressure was placed near the end of a slide and spread by means of the ground edge of a second slide. Care was taken to prevent the blood from accumulating at the ends or from spreading to the edges of the slide. The smears were stained with Wright's stain, and in most instances from 500 to 1,000 cells were counted. In a few cases in which the number of the leukocytes was very small, only 300 cells were counted. In all blood-smears, cells will be seen which are so distorted or disintegrated that their classification is impossible. Following the method of Carstanjen, these cells were counted in terms of 1,000, but were not included in calculating the percentages. When these cells were greater than 65 per 1,000, a second smear was made.

Since most of the cited investigations were made by means of the cover-glass method, it seemed advisable to obtain comparative results between the use of slides and cover-glasses. In the four determinations given below, the blood from the same case was counted, using successive drops of blood. The same number of cells was counted in each instance. The counts in Table 2 indicate that the results obtained by the two methods are practically the same:

TABLE 2.—BLOOD-CELL PERCENTAGES OBTAINED BY SLIDE AND COVER-GLASS METHODS

No.	Method.	Polymorpho- nuclear cells.	Lymphocytes.	Large mononu- clear and transi- tional cells.	Cells with eosin- ophilic granules.	Cells with baso- philic granules (Mast cells).
1	Slide .....	23.3	60.1	12	4	0.6
	Cover-glass ....	24.6	61	10.2	3.8	0.2
2	Slide .....	41.3	47.9	5	4.8	0.0
	Cover-glass ....	38.9	49.9	6	4.3	0.0
3	Slide .....	42.8	47.6	5	3.3	0.9
	Cover-glass ....	45.4	45.3	5.6	2.7	0.6
4	Slide .....	62	28.3	7.3	2.3	0.0
	Cover-glass ....	57.1	30.3	8.6	3.8	0.1

The maximum, minimum and average percentages shown by the differential counts are given in Table 3. In each instance the figures represent the results of five separate counts.

TABLE 3.—MAXIMUM, MINIMUM AND AVERAGE BLOOD-CELL PERCENTAGES BY DIFFERENTIAL COUNTS

AGE TWO DAYS TO TWO WEEKS					
	Polymorpho- nuclear neutro- phil cells.	Lymphocytes.	Large mononu- clear and transi- tional cells.	Polymorpho- nuclear eosinophil cells.	Mast cells.
Max. ....	40.2	55.9	16.2	9.7	0.5
Min. ....	26.6	47.9	5.1	3.0	0.0
Aver. ....	31.9	52.2	9.0	6.0	0.1
AGE TWO TO FOUR WEEKS					
Max. ....	37.5	61.9	13.4	6.8	0.8
Min. ....	19.5	51.3	3.6	2.6	0.0
Aver. ....	29.2	55.6	9.7	4.5	0.4
AGE ONE TO TWO MONTHS					
Max. ....	37.4	59.1	13.2	7.3	0.9
Min. ....	22.3	51.1	10.3	5.0	0.1
Aver. ....	29.7	51.3	11.7	6.0	0.4
AGE TWO TO SIX MONTHS					
Max. ....	33.4	65.8	13.5	4.5	0.6
Min. ....	19.5	54.3	6.4	1.0	0.0
Aver. ....	25.9	60.	10.9	2.5	0.3
AGE SIX TO TWELVE MONTHS					
Max. ....	35.9	58.5	12.2	4.5	0.8
Min. ....	24.6	50.5	7.3	0.0	0.1
Aver. ....	30.4	55.9	9.6	2.6	0.4
AGE ONE TO TWO YEARS					
Max. ....	39.7	58.8	11.7	6.0	0.5
Min. ....	27.5	45.3	6.7	1.6	0.0
Aver. ....	36.3	51.2	8.5	3.2	0.2
AGE TWO TO THREE YEARS					
Max. ....	44.3	55.0	11.3	6.0	1.2
Min. ....	33.2	43.5	5.0	0.5	0.0
Aver. ....	38.7	49.0	8.2	3.1	0.4
AGE THREE TO FOUR YEARS					
Max. ....	54.1	47.6	16.2	4.2	0.9
Min. ....	36.2	32.2	5.0	1.5	0.0
Aver. ....	44.7	39.1	11.2	2.8	0.5

TABLE 3—CONTINUED  
AGE FOUR TO FIVE YEARS

Max. ....	51.7	49.5	6.7	4.0	0.6
Min. ....	42.2	38.4	3.4	1.6	0.3
Aver. ....	48.5	42.1	6.0	2.6	0.3

AGE FIVE TO SIX YEARS

Max. ....	61.8	36.7	16.0	4.7	1.0
Min. ....	52.6	21.2	6.5	0.7	0.3
Aver. ....	56.5	29.9	10.0	2.5	0.6

AGE SIX TO SEVEN YEARS

Max. ....	61.3	34.1	15.7	4.7	0.6
Min. ....	52.3	24.5	8.1	0.1	0.0
Aver. ....	56.	30.4	10.8	2.2	0.2

AGE SEVEN TO EIGHT YEARS

Max. ....	72.0	39.1	15.2	3.5	0.2
Min. ....	45.2	21.1	6.7	0.0	0.0
Aver. ....	54.4	32.5	11.6	0.1	0.06

AGE EIGHT TO NINE YEARS

Max. ....	66.6	38.2	16.3	2.6	0.6
Min. ....	47.2	25.0	4.5	2.0	0.0
Aver. ....	56.4	31.0	9.8	2.2	0.3

AGE NINE TO TEN YEARS

Max. ....	64.2	36.1	9.6	4.3	1.3
Min. ....	53.2	18.1	6.0	1.5	0.1
Aver. ....	60.4	28.9	6.9	2.9	0.5

AGE TEN TO ELEVEN YEARS

Max. ....	69.5	35.2	8.5	3.5	0.7
Min. ....	54.4	20.5	6.5	1.0	0.0
Aver. ....	61.7	28.1	7.4	2.2	0.3

AGE ELEVEN TO TWELVE YEARS

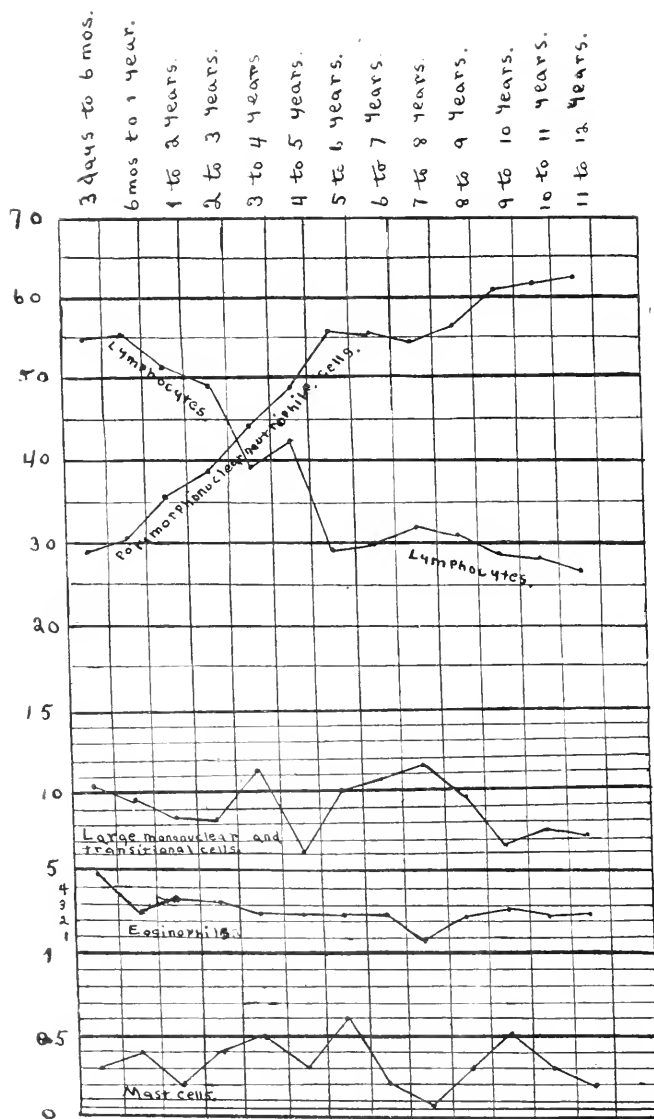
Max. ....	67.0	30.2	8.3	4.0	0.5
Min. ....	56.5	23.2	7.1	1.2	0.0
Aver. ....	61.8	27.7	7.3	2.5	0.2

The eosinophil cells were over 6 per cent. in seven of fifteen infants under 2 months of age; the highest percentage was 9.1. In two additional cases the percentage was greater than 5; in one 5.2 per cent., in another, 5.3 per cent. The highest percentages were found in infants between two days and two weeks of age.

In none of the fifty-five infants and children between 2 months and 12 years of age was the percentage of the eosinophil cells above 6. In two cases the eosinophil cells were 6 per cent. In all other cases the percentage was less than 5.

In comparison with the counts of Carstanjen these counts show a smaller percentage of polynuclear cells with a proportionately greater

percentage of lymphocytes in children under 5 years of age. The figures for children from 5 to 12 years of age are approximately the same. The percentages of the large mononuclear and transitional cells are also approximately the same, though for some ages there are slight differences ranging from 1 to 4 per cent.



Differential percentages of the leukocytes during the first twelve years of life.



A point of interest and of some clinical importance is the rather pronounced variation in the percentages of the different varieties of the leukocytes found in apparently normal infants and children of the same age. This variation is well shown in the counts of Carstanjen, Mosenthal, and those of myself. Moreover, these counts do not show the uniform increase of the polynuclear cells and decrease of the lymphocytes with advancing age. The plotted curve shows frequent breaks. Although there is every reason to consider that the change from the infantile to the adult blood type is gradual and progressive, yet it is very probable that within certain limits, the relative proportions of the different varieties of leukocytes undergo frequent variation as the result of influences which we are unable to appreciate. And lastly, it is not improbable that the rate of development of the blood may vary in different individuals, comparable to the variation often seen in the development of other tissues.

Owing to this variation in the percentages of the leukocytes, it is practically impossible to formulate definite percentages which can be considered normal for infants or children of a given age. It would perhaps be more accurate to state maximum and minimum percentages rather than the average.

#### SUMMARY AND CONCLUSIONS

1. In apparently normal infants from 3 days to 2 months of age, the eosinophil cells were frequently above the percentages normal for adults.
2. In normal individuals between 2 months and 12 years of age, when the known causes of eosinophilia were excluded, the eosinophil cells were rarely above 5 per cent. and never greater than 6 per cent., and were present in approximately the same relative proportions as in adults. It therefore seems only fair to conclude that there is no physiological eosinophilia in childhood; that 5 per cent. of eosinophil cells may be considered as the upper limit of normal, and certainly, more than 6 per cent. as pathological.

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## STUDIES OF MALARIA IN PANAMA: 1.—CLINICAL STUDIES OF MALARIA IN THE WHITE RACE \*

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During my service in 1905 and 1906 in Dr. Gorgas' wards in Ancon Hospital, I was particularly interested in certain phases of malarial infections, and I analyzed the cases admitted during the six months of my service with reference to the following points:

1. Incidence of malarial infections and mortality.
2. Results of examinations of blood for malarial parasites.
3. The relative value of several systems of quinin administration.
4. The time of day when malarial paroxysms occurred.
5. Malarial immunity.
6. The quinin test in differentiating malarial from other fevers.
7. Chronic malaria or malarial cachexia.

### INCIDENCE AND MORTALITY

There were admitted to the "white fever wards" during the six months 1,300 patients; 1,107 of these cases were clinically malarial. That is, at this time a little more than 85 per cent. of the morbidity among the whites was due to malaria. Among the 1,300 patients there were 15 deaths, 1.15 per cent. Four of these deaths were due to malarial fever (pernicious estivo-autumnal), and two to blackwater fever. If the latter be classed with malaria (and at present I think that it should be), there were six deaths in 1,107 malarial infections, a mortality of a little more than one-half of one per cent. (0.54 per cent.). Among 193 patients with other infections there were 9 deaths, 4.6 per cent., a mortality nine times as great as the malarial mortality.

### EXAMINATIONS OF BLOOD

As a routine procedure only one examination of blood for malarial parasites was made in each case; in special cases many examinations were made. Cover-glass films stained with Hastings' stain were found to be more reliable, both for the discovery of parasites and the differential diagnosis, than the unstained blood, especially when only one blood exam-

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\* Read at the meeting of the Medical Society of the Isthmian Canal Zone, April, 1910.

ination was made. Of the 1,107 cases diagnosed as malarial fever, parasites were found in the blood of 705, or 63.7 per cent. The large number of negative examinations could be accounted for by the fact that white patients had nearly always taken quinin before entering the hospital, and this quinin was sufficient to clear the peripheral blood of organisms, which were still present in sufficient numbers in the internal organs to produce more or less prolonged fever. The patients were given quinin immediately on admission, so parasites rarely reappeared in the peripheral blood. The percentage of positive examinations was greater, above 80 per cent., in a series of colored patients studied later. The colored patients do not take quinin so frequently before coming to the hospital.

The results of the blood examinations may be summarized as follows:

Total examinations.....	1,107	
Negative examinations.....	402—36.3 per cent.	
Positive examinations—		
Estivo-autumnal (E. A.) parasites.....	447—63.4 per cent.	705—63.7 per cent.
Tertian (Ter.) parasites.....	232—32.9 per cent.	
Mixed E. A. and Ter. parasites.....	26—3.7 per cent.	

No quartan parasites were found in this series.<sup>1</sup> The percentages given above for estivo-autumnal organisms is too small, and that for tertian correspondingly large, for, as I learned later, I made errors not infrequently, mistaking for tertian parasites some forms of the young estivo-autumnal parasites, viz., those very ameboid young forms which in stained specimens frequently show a considerable quantity of blue in their bodies. It is very risky to diagnose parasites as tertian when only very young forms can be found, for in tertian infections a careful search will almost invariably discover more advanced ages, invariably so when the young are fairly numerous. This is due (1) to the fact that tertian infections are usually multiple, and (2) to the fact that a group of tertian organisms sporulate not all at one moment, as most text-books lead one to believe, but over a period of from six to fourteen hours; so that where young forms are present, there are also present, belonging to the same group, either adult and presegmenting forms or parasites from one-fourth to one-third grown, which usually are easily classified. This rule is almost invariable, and is, I think, the most important point and the most constant criterion in the differential diagnosis between the young estivo-autumnal and tertian organisms.

1. *Later*.—Among colored patients the quartan parasite was found not infrequently. It occurs practically always in multiple groups in Panama, and sometimes produces a continued remittent fever. It rarely produces a typical quartan temperature, with sharp, short paroxysms.

## SYSTEMS OF QUININ ADMINISTRATION

In wards where such a large number of malarial patients are being treated it is necessary to adopt a routine system of administering quinin, varying the quantity and the method of giving it only in special cases. There have been a number of routine systems in vogue in the different wards of hospitals, the chief ones of which are as follows:

1. Quinin sulphate. 30 grains daily, 3 doses, 10 grains each, at 6, 8 and 10 a. m.
2. Quinin sulphate, 30-40 grains daily, in 5-grain doses, every four hours, with two additional doses of 5 grains each, timed so as to anticipate the paroxysms in obstinate cases.
3. Quinin sulphate. 20 grains daily, 2 doses, 10 grains each, at 6 and 8 a. m.
4. Quinin sulphate. 30 grains daily, 3 doses, 10 grains each, morning, noon and night.
5. Quinin sulphate. 30 grains daily, 2 doses, 15 grains each, at 8 and 11 a. m.

The first three systems of administration were used in the present series of cases. An analysis of 645 cases was made in order to determine if possible the relative value of the three systems of administration. Pernicious cases were excluded, as they were always treated with intramuscular injections of quinin. The criteria used in judging the several systems were:

1. The average duration of the febrile period.
2. The comfort of the patient with reference to cinchonism and the taking of medicine.
3. The frequency of vomiting.
4. The number of patients requiring intramuscular injections of quinin.
5. Economy in routine ward work.
6. Relapses.

By "duration of the febrile period" is meant the time that elapsed from admission until the temperature remained permanently at or below 99 F. The results of treatment by the first three systems of quinin administration are shown with reference to the febrile period in the following table. By "clinical malaria" is meant those cases in which parasites were not found.

TABLE 1.—RESULTS OF TREATMENT BY THREE DIFFERENT SYSTEMS OF ADMINISTRATION OF QUININ WITH REFERENCE TO FEBRILE PERIOD

System.	—E. A.—		—Tertian—		—Clinical—		Total Cases.
	Cases.	Hours of Fever.	Cases.	Hours of Fever.	Cases.	Hours of Fever.	
1	96	55 3/4	51	37 1/3	69	40 1/2	216
2	123	53 1 2	41	37 1/2	102	40 1 2	266
3	66	70 1 6	41	45	56	43 2/3	163

The duration of the febrile period was approximately equal under the first two systems. Under System 3, however, the fever of estivo-

autumnal infections was nearly one-third longer; of tertian, one-fifth longer; and of clinical cases, one-thirteenth longer. These patients were far more uncomfortable than the others, the symptoms being much more marked and the fever of many prolonged. Therefore System 3 (20 grains of quinin given in two doses of 10 grains each at 6 and 8 a. m.), may be considered inadequate for routine use in male adult wards.

The choice between Systems 1 and 2 must be based on other criteria than the febrile period. Under System 1 the discomfort of cinchonism was greater, but, on the other hand, the patient took only three doses of quinin during the day, whereas under System 2 he had to be awakened at night and he took six to eight doses of quinin, a not unimportant consideration, especially when quinin in solution is being used. The advantage here then seems to be with System 1. More important is the fact that under System 1 vomiting was less frequent and, therefore, intramuscular injection of quinin was not so frequently demanded. In addition System 1 makes for economy of work in the ward routine, for a considerable amount of time is saved when among forty patients each is given three doses of medicine during the morning hours (120 doses) instead of six or eight doses (240 or 320) distributed throughout the day and night.

The most valuable criterion by which to judge the matter would be the percentages of relapses under the different systems. Unfortunately the data regarding this point is unreliable, for during a relapse a patient might have entered another hospital on the Isthmus, or have been treated at a dispensary, or have remained in his quarters and taken quinin. The relapses are frequently mild, and sometimes a patient will continue his work while taking quinin. As far as the data available go, evidence is afforded in favor of the first system. Under this system only 12 per cent. of 229 patients returned to the hospital within three months with relapses of fresh infections. Of 273 patients treated under System 2, 16 per cent. returned within three months. That the figures are not altogether reliable, however, is shown by the fact that of 173 patients who were given only 20 grains (System 3) during the morning hours, only 7.5 per cent. returned within three months.

Altogether, I think that the evidence is strongly in favor of the routine administration of quinin to male adult malarial patients according to System 1. In my opinion, it is both better for the patients and is preferable for administrative reasons. With a slight modification, I have adopted the system for my wards in Colon Hospital. The modification constitutes System 5, mentioned above, and consists in giving the 30 grains in two doses of 15 grains each at 8 and 11 a. m. These hours are

more convenient for the nurses, and the reduced number of doses of quinin renders its administration less disagreeable to the patients, especially to those taking quinin in solution.

In all ordinary cases of malaria this dosage is sufficient and the method effectual, and, excepting in pernicious infections, I practically never vary it. Under this system injections of quinin are rarely necessary.

I have not yet compared System 4 with other systems, but at Colon Hospital I have for analysis and comparison large series of cases treated according to Systems 4 and 5. My impression is that System 4 has no advantage over the other, but rather the contrary.

The method of quinin administration, especially in estivo-autumnal malaria, usually advised by writers on the subject, is that of System 2, for by keeping a uniform solution of quinin in the blood throughout the twenty-four hours, such as would be obtained by this system, parasites sporulating at any hour would be subjected to a fairly strong solution at a time when they are free in the plasma and most susceptible to quinin. It was surprising, therefore, when this system did not yield better results than that in which a much stronger solution of quinin in the blood was begun during the morning hours, reached its maximum probably about 12 p. m., and gradually decreased to a minimum before 6 a. m. the following day. We know that quinin is eliminated rapidly in the urine. Cushny states that when a 10-grain dose is given by mouth, half of it is excreted within six hours. One would anticipate, therefore, that under the first system of quinin administration fever due to parasites sporulating during the night hours might recur indefinitely, for the parasites then would be exposed to a relatively weak solution of quinin. Why this did not happen and why vomiting was less marked with the larger doses of quinin were interesting questions for study, and an attempt was made to find an answer to them by analyzing 532 paroxysms with reference to the time of day at which they occurred. The hour of maximum temperature was found to be the most feasible one for indicating the time of occurrence of paroxysms. Moreover, it presumably indicates approximately the time of sporulation of the largest number of parasites.

#### TIME OF DAY WHEN MALARIAL PAROXYSMS OCCURRED

TABLE 2.—HOURLY OF MAXIMUM TEMPERATURE OF MALARIAL PAROXYSMS

Infection.	8 a. m.	12 m.	4 p. m.	8 p. m.	12 p. m.	4 a. m.	Total.
Estivo-autumnal . . . . .	11	46	121	63	24	16	281
Tertian . . . . .	5	19	34	13	8	0	79
Clinical . . . . .	18	36	77	18	14	9	172
Total . . . . .	34	101	232	94	46	25	532
Percentage . . . . .	6.4	19.	43.6	17.7	8.6	4.7	100.

It is seen at once that this striking table does throw light on the questions suggested. The maximum temperature in 80.3 per cent. of the paroxysms occurred at the hours of 12 m., 4 and 8 p. m.; the greatest number, 43.6 per cent., at 4 p. m. There is practically no variation between the different groups—estivo-autumnal, tertian, and clinical malarial. The temperature is lowest from 4 a. m. to 12 m., and this means that the patients then are in better condition with less irritable stomachs than at other hours. Therefore, quinin is taken with greater ease, is better borne, and presumably absorbed more readily. This explains the fact that with the larger doses given at only two-hour intervals there is less vomiting than there is with doses half the size given at four-hour intervals; and it demonstrates also that the primary factor in the vomiting of malaria is not irritation of the stomach by quinin but the malarial poison itself. The table shows also that when large doses of quinin are administered during the morning hours a concentrated solution in the blood is obtained during the period preceding and including the rise of fever; that is, at a time when the largest number of parasites are sporulating and are most susceptible to quinin.

As for the parasites that sporulate during the night hours, they are as a rule comparatively few in number, judging by the temperature curve, and they appear to be killed by the quinin still uneliminated, or else the concentrated blood-solution during the day kills them while they are still in the intracorpuscular stage. I am quite in agreement with the view that quinin can do this, but its parasitocidal power is not, I think, nearly so marked as when it acts on the free merozoites.

My table regarding the hour of malarial paroxysms is not in agreement with Troussseau<sup>2</sup> and Manson.<sup>3</sup> The latter makes the following statement when discussing the differential diagnosis between malaria and liver abscess: "In hepatic abscess the fever occurs generally, though not invariably, in the late afternoon or evening. In malarial fever the paroxysm may, and generally does, occur earlier in the day." Elsewhere he says: "Two-thirds of agues come off between midnight and midday." The term "agues" is here "applied only to intermittents having a pronounced rigor stage," i. e., tertian and quartan infections. My table, however, is in agreement with Koch,<sup>2</sup> who found that the "malignant tertian" fever almost without exception occurs at midday or during the first hours of the afternoon; and with Craig,<sup>4</sup> who states that the parox-

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2. Cited by Scheube in *Diseases of Warm Climates*. F. Blakiston's Son & Co., 1902, Philadelphia.

3. Manson: *Tropical Diseases*. William Wood & Co., 1909, New York.

4. Craig: *The Malarial Fevers*. William Wood & Co., 1909, New York.

isms in all forms occur usually in the afternoon. In my cases, afternoon was the time when paroxysms occurred most frequently; and in my tertian infections, "agues," the maximum temperature was reached in 60 per cent. of the paroxysms at 4 and 8 p. m.; that is, nearly two-thirds of the "agues" occurred between 12 m. and 8 p. m.

#### MALARIAL IMMUNITY

Immunity may be natural or acquired, and either natural or acquired immunity may be absolute or relative. My experience has led me into a study of only acquired relative immunity in the malarial fevers. Two series of cases have been analyzed with a view to obtaining data on this important question. The analysis was based on the duration of the febrile period, according to the number of previous attacks of malarial fever.

Series 1. Estivo-autumnal infections, 138; tertian, 54. Patients all treated with 30 grains of quinin daily, in 10-grain doses, at 6, 8 and 10 a. m. (System 1.)

Series 2. Estivo-autumnal infections, 110; tertian, 38. Patients all treated with 30 to 40 grains of quinin daily, given in 5-grain doses throughout the twenty-four hours. (System 2.)

TABLE 3.—SHOWING DURATION OF FEVER ACCORDING TO NUMBER OF PREVIOUS ATTACKS

SERIES I			
Infection.	Number of Previous Attacks of Fever.	Number of Cases in Groups.	Average Hours of Febrile Period.
Estivo-autumnal . . . . .	0	37	61.8
	1	46	46.
	2	22	46
	3	14	48
	4 or more	19	33
Tertian . . . . .	0	4	30.5
	1 or 2	27	24.5
	3 or more	23	17
SERIES II			
Estivo-autumnal . . . . .	0	42	68.6
	1	24	47
	2	24	44.2
	3	14	44
	4 or more	6	28
Tertian . . . . .	0	16	55.6
	1 or more	22	26.

In the estivo-autumnal infections of both series a marked reduction in the febrile period is noted after the first attack, and then there is slight reduction, or none, until one reaches the group that has had four or more previous attacks. The tertians of Series 2 are very striking, for in them the duration of the febrile period is decreased more than half



after the first attack. In the tertians of Series 1 the number of patients who had no previous fever is too small to be of much value, but here, also, a decreased febrile period is observed after the first attack and a further decrease after three or more attacks.

These tables, therefore, furnish distinct evidence of acquired relative immunity conferred by former attacks of malarial fever in adult white males from the United States and Europe. This immunity is not, however, an immunity to infection, for malarial parasites were found in all these patients, some of whom had no fever while in the hospital. It is rather a tolerance for the malarial poison or toxin. Furthermore, one who watches the cases and compares carefully the symptoms in cases belonging to the different groups above cannot but be struck by the increasing mildness of the symptoms with more numerous former attacks of fever, and with the greater ease with which the peripheral blood, at least, is cleared of schizonts. For instance, two patients were admitted at the same time with heavy infections of estivo-autumnal parasites, which were about equally numerous in the two cases. The first patient had had no previous fever, the second had had one attack. The first patient ran a severe course with high remittent fever, the period of which lasted five days; his symptoms were severe headache, malaise, nausea, vomiting, and it was necessary to resort to intramuscular injections of quinin. Parasites in the peripheral blood were persistent. The second patient had mild symptoms which were relieved by the second day; he was able to take quinin by mouth without difficulty, and his intermittent temperature reached normal on the third day and remained normal. Parasites quickly disappeared from the peripheral blood. This rule, however, does not always hold good, and severe attacks do occasionally occur in patients who have been subject to previous malaria; that is, tolerance is not invariably established.

Regarding acquired relative immunity, Craig<sup>4</sup> remarks: "This immunity, however, is often gained at the expense of the vitality of the individual, and the penalty inflicted is a chronic malarial cachexia, which markedly lowers the health of these immunes." This is a view that I, also, held when I first came to Panama, but subsequent evidence led me to the contrary opinion. In a paper<sup>5</sup> read before this Society in January, 1907, I presented the results of a study that Zeiler and I had made of the hemoglobin of colored laborers. The cases of uncomplicated malaria were grouped according to the number of previous attacks of fever, and Table 4 was constructed with reference to hemoglobin estimations:

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5. Brem, W. V., and Zeiler, A. H.: THE ARCHIVES INT. MED., 1910, v, 569.

TABLE 4.—SHOWING HEMOGLOBIN ESTIMATIONS IN CASES GROUPED ACCORDING TO NUMBER OF PREVIOUS ATTACKS

Number Previous Attacks.	Number Cases.	Number Cases of Anemia, 60 Per Cent or Less.	Average Hb Per Cent.
0	49	1	80.4
1 or 2	39	5	75.
3—5	23	7	65.
6 or more	19	2	72.

As one would anticipate, the hemoglobin percentage fell uniformly with the first attacks of fever, and the relative number of cases of anemia became greater. When, however, the group of patients who had had "6 or more" previous attacks was reached, an unexpected rise of hemoglobin occurred and the relative number of cases of anemia markedly decreased. I remember well this last group of patients, usually men who had been unprotected for several years on the Isthmus. They were West Indian negroes from Barbadoes, where no malarial fever exists. I anticipated finding in such patients marked anemia, the condition of cachexia, but I was astonished at finding them in good condition, with spleens not enlarged.

Regarding this tolerance for the malarial poison, it seems safe to say that after one or more malarial infections (1) the fever of subsequent attacks is more readily controlled by quinin, (2) the symptoms are milder, (3) parasites are killed out, at least from the peripheral blood, more readily, (4) after numerous infections with increasing tolerance the average hemoglobin percentage tends to increase and the number of cases of anemia decrease, and (5) tolerance is not invariably acquired and occasional patients will be met who have had malaria frequently and who, nevertheless, will have very severe attacks.

#### QUININ TEST FOR DIAGNOSIS

The former tables showing the decreasing duration of the febrile period with more numerous attacks of malaria have a bearing on the quinin test to differentiate malarial from other fevers. Table 5 shows the number of estivo-autumnal infections in the different groups of Table 3, Series 1 and 2, in which the fever continued three days or more. In each case the duration of the fever in days and hours is shown.

Since the results are approximately the same in the estivo-autumnal infections of the two series, they may be summed up together. If a patient has an estivo-autumnal infection and has had no previous malaria, the chances are about 2 to 1 that his fever will cease within three days; 4.5 to 1, if he has had 1, 2 or 3 previous attacks of fever; 24 to 1, if he has had 4 or more attacks. In first attacks of malaria the fever not

infrequently continues intermittently for four, five, six or even, rarely, eight days, with rudimentary paroxysms after three days; and in secondary attacks it occasionally continues from three to five days. I am in doubt about the cases in which the fever of secondary attacks continued six, seven or eight days, and I strongly suspect that there were complications that I overlooked. At any rate, these cases are so rare that they may be disregarded for practical purposes.

TABLE 5.—(E. A.'s OF TABLE 3.)—SHOWING THE RELATION BETWEEN THE NUMBER OF PREVIOUS ATTACKS OF FEVER AND THE NUMBER OF PROLONGED ATTACKS

SERIES I										
Number previous attacks.	0		1		2		3		4 or more	
Total number cases each group .....	37		46		22		14		19	
	Days.	Hrs.	Days.	Hrs.	Days.	Hrs.	Days.	Hrs.	Days.	Hrs.
Duration of Fever	7	18	3	20	6	14	8	14	3	0
	6	0	3	18	4	0	3	0		
	5	18	3	14	3	20				
	5	4	3	14	3	0				
	4	22	3	14						
	4	18	3	12						
	4	6	3	4						
	3	18	3	0						
	3	16								
	3	14								
	3	14								
	3	12								
	Number cases with fever 3 or more days.....	12		8		4		2		1
Frequency of cases with fever, 3 or more days..	1 in 3		1 in 6		1 in 5.5		1 in 7		1 in 19	
SERIES II										
Number previous attacks.	0		1		2		3		4 or more	
Total number cases each group .....	42		24		24		14		6	
Duration of Fever	5	0	4	0	4	12	5	6	0	
	4	16	3	12	3	20	4	12		
	4	12	3	4	3	4	3	0		
	4	12	3	0	3	0				
	4	12			3	0				
	4	8								
	4	0								
	3	18								
	3	16								
	3	12								
	3	12								
	3	12								
	3	8								
	3	4								
	3	4								
	3	2								
	3	0								
Number cases with fever 3 or more days.....	17		4		5		3		0	
Frequency of cases with fever, 3 or more days..	1 in 2.5		1 in 6		1 in 5		1 in 5		0 in 6	

The febrile period of no tertian infection of the fifty-four in Series 1 (Table 3) continued for three days. Of thirty-eight tertians of Series 2, the fever of four continued for three days or more. These were among the early cases, and were, I feel sure, cases in which estivo-autumnal organisms were erroneously diagnosed tertian.

In stating that the duration of the febrile period was so many days, it is not, of course, intended to imply that the fever was high or continuous during this time. On the contrary, there were almost always marked remissions or intermissions and when fevers did not terminate abruptly soon after the administration of quinin was begun, the undulations became less and less marked until the temperature remained normal. One might think that this marked remittent or intermittent type of fever should assist in the diagnosis during the first three days, but it does not. In the first place the remissions or intermissions do not always occur within three days, and if the patient has had no previous malaria, the temperature may be not only continuous but rising. In the second place, quinin in the doses given has a marked antipyretic effect in other infections, and as a result I have repeatedly seen intermissions in typhoid and other fevers. These drops of temperature are usually associated with remissions of symptoms. Even in pneumonia, pseudocrises are frequent on the day after admission to the hospital when quinin is being given, and the temperature, without physical signs and other phenomena, might be misleading. Indeed a form of "pneumonic malaria" has been described by no less an authority than Scheube.<sup>2</sup>

Regarding the quinin test, however, it may be said that in primary attacks if the temperature continues high on the fourth day one may safely consider that the fever is not malarial, and the test may be discontinued. If a remittent or intermittent fever continues unabated for four days it is not of malarial origin. If a marked remission occurs on the fourth day in the course of a continued fever and if there is a decrease in the fastigium, quinin should be continued, and if the temperature remains normal after the sixth or seventh day, it is probable that the fever has been a rare and unusually prolonged malarial fever. If a blood culture or positive agglutination reaction has not been obtained, however, there may be still a question as to whether one has dealt with a long malarial or a short typhoid attack. Even in Colon Hospital, where routine examinations of blood are made and where routine blood cultures are taken in all undiagnosed fevers continuing more than three days, we have sometimes been left in doubt. As a rule, then, in first attacks four days is sufficient for the test, and six days is the maximum time to be allowed it.

If the patient has had malaria before, the remissions and intermissions will be more marked and three days will be usually sufficient time to persist in the test, four days the maximum time.

All tertian fevers are controlled by quinin in these doses within three days.

The statements are made on the assumption, of course, that the quinin has been given in a form readily absorbed, that it has been absorbed, and that the patient has been kept at rest in bed. In one instance the temperature of a colored patient who had an estivo-autumnal infection continued remittent and ranged between 100 and 103 F., for more than a week. The patient stated that he had taken his quinin and the nurse had seen him swallow it. But when he was watched it was found that he slipped out of the ward after swallowing his quinin, and he was caught with his finger down his throat in the act of stimulating vomiting. His elevated temperature ceased immediately when this practice was stopped. Another patient with estivo-autumnal malaria had a long-continued remittent fever. On investigation it was found that though the order for quinin was entered on the chart the nurse had neglected to enter it on the medicine list, and the patient had received none. This elevated temperature, also, ceased immediately when quinin was given. A third patient with a double tertian infection and who was getting quinin in solution had chills every evening and his temperature at 12 m., reached 104 or 105 for about ten or twelve days. We could not understand why this should be so, for the patient seemed fairly intelligent and declared that he was swallowing his quinin regularly and was not vomiting. The nurse had watched him closely and stated that he swallowed his quinin, did not vomit it, and did not leave his bed afterward. However that may be, he was given an intramuscular injection of quinin, and there were no further paroxysms. It is certain that the quinin was not absorbed, and I suspect that it was not swallowed, for we have repeatedly detected colored patients holding the solution in the mouth in order to spit it out as soon as the nurse passed by. In these persistent fevers, absorption of the quinin should be ascertained by testing for its presence in the urine.

Tablets and pills of quinin sulphate are notoriously insoluble, and on the wards we have frequently found them unchanged in the feces. They have often been found in the intestines at autopsy. Tightly packed quinin in capsules has also been known to pass through the intestines with the gelatin capsule dissolved off but the quinin retaining its capsule mould. It is possible, also, that in malaria the acidity of the gastric juice is often diminished to such an extent that the sulphate of quinin is

not rendered soluble and that much of the insoluble salt passes through unabsorbed.

All of these points tend to discredit the therapeutic test for malaria, which at best is a rather undesirable procedure. It is, however, one that we must resort to frequently here where malaria is so prevalent, and where each day's delay is a loss both to the patient and to the Commission. Many patients on admission have taken sufficient quinin to rid the peripheral blood of parasites while they are still present in sufficient numbers in the internal organs to produce a fairly prolonged fever, as may be seen by reference to the group, "clinical malaria," Table 1. In these cases it would not be fair to withhold quinin for one or several days until parasites reappeared. Moreover, in Panama even when parasites are present, the administration of quinin is a diagnostic measure, because a considerable proportion of all our typhoid and other infections are complicated by malaria, and the malarial element often has to be eliminated before the other condition can be diagnosed with certainty. In regions where malaria is not common, however, I should not recommend the test if it is possible to make repeated blood examinations for malarial organisms, blood cultures and agglutination tests.

Rest in bed is an important adjunct to the test, and is second only to quinin in the treatment of malaria. In one instance a nurse took 20 grains of quinin daily for three weeks, during which time she had fever daily, but continued on duty. She then entered the hospital and an examination of her blood showed numerous estivo-autumnal parasites. She was put to bed and given the same quantity of quinin that she had been taking. Her fever ceased promptly, and no parasites were present on the third day. Numerous cases similar to this one have come under my observation.

#### CHRONIC MALARIA AND MALARIAL CACHEXIA

Chronic malaria and malarial cachexia are terms that are loosely used, especially in malarious regions, and that cover many sins of omission on the part of physicians in charge of such cases. These authoritative terms for years effectually obscured the infection of uncinariasis throughout the southern states, an infection discoverable by a most simple procedure. Indeed it is difficult now to understand how the infection escaped so long. Kala-azar and trypanosomiasis likewise escaped for years under the guise of chronic malaria, and numberless patients with incipient tuberculosis have lost their chance of recovery because of the looseness with which the malarial terms are employed and the readiness with which they are accepted by the laity. Though I recognize a cachectic condition resulting

from neglected malarial infections. I do not think that the independent diagnosis of chronic malaria or malarial cachexia should ever be made. The terms may be used in elaboration of the diagnosis of malarial fever, but there should be proper evidence that malarial infection exists. In five years' service in Panama, during which there have been about 15,000 cases of malaria under my care, I have never used the terms and have felt no inconvenience on account of their exclusion. I am sure that their exclusion has caused us to seek more earnestly for diagnoses in many obscure cases than we would have done had such an easy way out of the difficulty been countenanced. The terms describe a condition, not a disease, and the disease itself may almost invariably be proved or disproved if proper examinations are conducted. If repeated examinations fail to demonstrate malarial parasites the condition is probably not malarial. If, in the same case, physical and other examinations fail to demonstrate another disease (as tuberculosis, uncinariasis, cirrhosis of the liver or chronic nephritis—the most frequent ones) then in malarious regions, one may try the quinin test. But it must be remembered that, if due to malaria, the condition is the result of either numerous infections or a long-standing infection, and that considerable tolerance has been acquired. Therefore, one should get prompt results from the administration of the drug. It is safe to say that if within three days after quinin is begun all symptoms, other than may be accounted for by anemia, do not cease entirely, then the condition is not due to malaria. Moreover, I have found that postmalarial anemia is a condition from which one recovers with remarkable rapidity simply with quinin, rest and good food, and without resort to arsenic and other drugs usually recommended for postmalarial treatment. Therefore, I would say, also, that any chronic anemic condition that does not improve rapidly with the patient at rest and under quinin treatment is not of malarial origin, and the diagnosis must be sought elsewhere.

#### SUMMARY

1. In the "white fever wards" of Ancon Hospital, during 1905 and 1906, 1,107 of 1,300 patients were malarial, a morbidity of 85 per cent. The malarial mortality was 0.54 per cent.; the mortality from other diseases 4.6 per cent., or about nine times that of malaria.

2. Malarial parasites were found in the peripheral blood of 705 patients, or 63.7 per cent. of the malarial cases. The estivo-autumnal parasite alone was diagnosed 447 times, or in 63.4 per cent. of the positive cases; the tertian alone, 232 times, or in 32.9 per cent.; mixed infections with estivo-autumnal and tertian organisms were found in 26 cases, 3.7 per

cent. No quartan organisms were found in this series. The estivo-autumnal percentage is probably slightly too small, and the tertian too large.

3. Three systems of quinin administration were tested:

1. Thirty grains daily, 3 doses of 10 grains each, at 6, 8 and 10 a. m.
2. Thirty to 40 grains daily, given in 5-grain doses every 4 hours, with 2 extra doses of 5 grains each given in obstinate cases before the approximate time for the onset of paroxysms, at 10 a. m. and 2 p. m.
3. Twenty grains daily, 2 doses of 10 grains each, at 6 and 8 p. m.

The febrile period was approximately equal under Systems 1 and 2; it was much longer under System 3. All things considered, System 1 seems to be preferable for the treatment of ordinary infections in male adults.

4. The great majority of malarial paroxysms, both estivo-autumnal and tertian, occur between the hours of 8 a. m. and 8 p. m.

5. Acquired partial immunity or tolerance for the malarial poison is marked after the first infection. The febrile period and the severity of the symptoms decrease markedly after the first attack, remain approximately stationary in the second, third and fourth attacks and then undergo another marked decrease.

6. For the quinin diagnosis test, the drug should be given in the doses of System 1 or 2 to male adults. In other cases the quantity may be regulated by the weight of the patient. In first attacks of malaria, the fever of two out of three estivo-autumnal infections will reach and remain normal within three days. If a marked remission and a much-decreased fastigium do not occur on the fourth day, the fever is not malarial and quinin may be discontinued. If a remittent or intermittent fever continues unabated for more than four days, it is not of malarial origin. First attacks may show mild or rudimentary paroxysms of fever for six, seven or eight days. Ordinarily one should be able to draw conclusions from the test in four days or less, though rarely six days may be needed. In secondary attacks of malaria, fever usually ceases within three days, and a remittent or intermittent fever that persists unabated for three days is not malarial. Four days is the maximum time to persist in the test. All tertian infections are controlled within three days.

Great care must be used to insure the absorption of quinin, and the patient must be kept at rest in bed.

7. Chronic malaria and malarial cachexia are much-abused terms; they describe a condition and not a disease, and should be used only in elaboration of a diagnosis of malarial fever, for which proper cause should be shown. If parasites are not demonstrable and if careful examinations appear to exclude other diseases, the quinin test may be used in malarious



regions. If an anemic (cachectic) condition is due to malaria, a partial immunity or tolerance has been acquired, and quinin causes a rapid cessation of fever and other symptoms. If these do not disappear within three days, or if the anemic condition does not improve rapidly, malaria is not the origin of the trouble, and another diagnosis must be sought. In using the test, the patient must be kept at rest in bed, and the absorption of quinin must be assured.

In conclusion, I wish to thank Col. W. C. Gorgas, Chief Sanitary Officer, for permission to publish this paper.

# PERNICIOUS ANEMIA MISTAKEN FOR AMEBIC ULCER- ATIVE COLITIS

WITH OBSERVATIONS ON THE IPECAC TREATMENT\*

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A case of pernicious anemia presenting a number of unusual features, among them some facts of interest in connection with the diagnosis and treatment of amebic colitis, seems worthy of record.

## REPORT OF CASE

*History.*—The patient, a man aged 48, married, without children and having a good family history, was born in Tennessee, but for the past eight years had lived on fruit plantations in Cuba and Porto Rico. Beyond occasional indefinite stomach disturbances there had never been a significant illness.

*Present Illness.*—This began in June, 1909, when there were loss of appetite, drowsiness, fatigue and loss of weight. In September, 1909 there was a diarrhea with mucus, but no blood. This was relieved by a milk diet, but recurred at intervals afterward, there being four to eight watery movements daily without pain or tenesmus. The abdomen was tender, particularly above the umbilicus. Vomiting occurred only twice. Fever had never been present. After Oct. 26, 1909, the patient had to remain in bed. November 1, a thorough examination in Porto Rico gave negative findings, except that free hydrochloric acid and pepsin in the stomach contents were said to be much diminished. In December there was some improvement, but after Jan. 3, 1910, the condition became steadily worse. About February 1 a roundworm was passed in the stool. The patient arrived in New York February 11, after a severe voyage, two days late, and, as he said, "half starved." Diarrhea, from which he had been free at the beginning of the trip, returned. Milk diet seemed the only sort that agreed with him. The patient's previous weight was 136 pounds; Jan. 1, 1910, it was 104 pounds, on arrival in New York it was much less, though the patient was too ill to be weighed.

*Examination.*—This showed a man extremely emaciated, with sunken cheeks; the ribs were all prominent. The expression was dull and weak; the lips were dry and the tongue was clean. The patient's mentality was slow. The color was pale, but not lemon-yellow. The heart was not enlarged; its action was regular and rate 88. The first sound was short, the second normal, and the second aortic louder than the second pulmonic. There were no murmurs. The radial arteries were nodular: the systolic pressure 100, and diastolic, 65. The lungs were normal. The abdomen was slightly prominent when compared with the general emaciation, and felt doughy. There was gurgling everywhere and tenderness over the lower half, most marked on the left. The liver and spleen were not large. The kidneys were not palpable. There were no enlarged superficial

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\* From the service of Dr. T. C. Janeway, St. Luke's Hospital.

lymph-nodes. Rectal examination showed nothing abnormal. Ophthalmoscopic examination was unsatisfactory.

February 12, the stool was examined. This was brown, fluid, offensive and showed mostly debris and bacteria, without pus or blood. During an hour's search, three actively motile amebas were found. These were not studied in detail, but being of the usual size and degree of motility of the *Amoeba dysenteriae*, they were considered such. The hemoglobin was 20 per cent., the polynuclears were 29 per cent., small lymphocytes 60.5 per cent., large lymphocytes 10.5 per cent. The smear showed no leukocytosis, but there was marked pallor of the red cells, anisocytosis and poikilocytosis and three normoblasts.

February 13 there was tenderness in the left iliac fossa, umbilical and epigastric regions with gurgling throughout. A diagnosis of chronic ulcerative colitis was made and the patient removed to St. Luke's Hospital. The hemoglobin was now 18 per cent., the red cell count, 1,352,000; index, 0.66; leukocyte count, 4,000; polynuclears, 49 per cent.; lymphocytes, 48 per cent.; eosinophils, 3 per cent., with marked poikilocytosis, anisocytosis and one normoblast. The urine was acid, had a specific gravity of 1.019 and showed a faint trace of albumin, but no sugar. Urates and uric acid were present.

*Treatment and Course of Disease.*—The ipecac treatment as described by Simon<sup>1</sup> was begun.

February 13: One ounce of castor oil was given.

February 14: Three hours after the evening feeding fifty grams of ipecac were given in ten five-grain pills coated with 1 16 inch phenyl salicylate (salol). The amount of ipecac was diminished by five grains each succeeding day.

February 17: There was nausea, increasing weakness and continued diarrhea.

February 18: The red cells were 840,000; hemoglobin 18 per cent; index 1.0; the leukocytes numbered 2,800, the polynuclears were 44 per cent; the lymphocytes 56 per cent.

February 19: Two ipecac pills were recovered from the stool, the phenyl salicylate coating only having dissolved. The urine was dark and contained phenol. Keratin-coated ipecac pills were given, 35 grams in all, and were followed in the night by several attacks of vomiting.

February 21: Ipecac was stopped and four ipecac pills with the phenyl salicylate coating partially dissolved appeared in the stools. The urine continued to be dark in color.

February 23: The red cells were 700,000, the hemoglobin 14 per cent., the index, 1. The leukocytes were 2,200, the polynuclears 40 per cent., lymphocytes 59 per cent., eosinophils 1 per cent. Marked macrocytosis, many microcytes and poikilocytes and slight basophilia were noted.

February 24: The red cells were 720,000, the hemoglobin 14 to 17 per cent. This rapid loss of blood seemed an indication for transfusion. A donor showing no hemolysis was chosen and the patient was transfused by Dr. Lyle for thirty minutes. He returned from the operating-room in poor condition, having a pulse of 120 and respirations 25. During the operation the hemoglobin rose from 23 per cent. to 35 per cent. and the red cells to 1,692,000. The smears showed many normoblasts and megaloblasts, some of the latter showing mitosis, and an active phagocytosis of the red cells, which features are to be reported in detail elsewhere by Dr. Hopkins of St. Luke's Hospital.<sup>2</sup> At 4:30 p. m., two hours after the transfusion, there was restlessness and delirium, with tendency to stupor, a slightly stertorous respiration, 18 per minute, and suggesting Kussmaul

1. Simon, S. K.: Amebic Dysentery, Jour. Am. Med. Assn., 1909, liii, 1526.

2. Hopkins, J. Gardner: Phagocytosis of Red Blood-Cells.

breathing. The temperature was 102.6 F., the pulse 124. There was no response to stimulation by strychnin and caffein. At 7:30 p. m. there was coma and stertorous respiration. At 10 p. m. the patient died.

*Autopsy.*—A partial autopsy next morning showed the following: Liver: Slight congestion and numerous deposits of hemosiderin. Spleen: Slightly enlarged, markedly congested, moderate deposits of hemosiderin. The sinuses were distended and the pulp packed with red blood-cells. Intestines: Normal throughout except a slight hyperplasia of the solitary lymph follicles and a few petechiae. Bone-Marrow: This was taken from the middle of the shaft of the femur and of the humerus. It was pink in color, showing red dots. Microscopically there were small hemorrhages, islands of myeloid cells and extensive phagocytosis of red cells. There were also a few normoblasts and megaloblasts. The sinuses of the mesenteric lymph-nodes contained numerous phagocytes.

Three points of unusual interest are brought to attention in the study of this case: The first is the effect of transfusion of blood from a donor, showing no hemolysis, in the apparent rapid thrombosis of certain of the cerebral arteries, with the completion of the blood-picture of a pernicious anemia; the second point concerns the diagnosis of amebic ulcerative colitis; the third, its treatment by the ipecac method.

A patient resident in a tropical country giving a history of diarrhea, emaciation and weakness, without fever, showing a pallor not of the lemon-yellow type, abdominal tenderness, a blood-picture that, until its latest antemortem development, might have been that of a secondary anemia, and the presence of amebas in the stool gave evidence enough to justify the diagnosis first tentatively made.

The importance and the difficulty of differentiating *Entamoeba coli* and *Entamoeba histolytica*, emphasized by this instance and the differential points given by Schaudinn,<sup>3</sup> and confirmed by Craig,<sup>4</sup> may well be repeated. *Entamoeba coli* may be found in 60 per cent. of stools of normal individuals after giving a saline cathartic. The ectoplasm of *Entamoeba coli* is not well differentiated from the endoplasm, one being as refractile as the other except on the formation of the pseudopodia, which are less refractile than the cell body. The nucleus is distinct, vesicular, centric, with a thick limiting membrane and several nucleoli. Multiplication is by simple fission or by schizogony, with formation of cysts, in which resting stage a new host may be infected.

The ectosarc of the *Entamoeba histolytica* is sharply delimited from the endoplasm by being much more refractile, denser and firmer, so that the

3. Schaudinn: Untersuchungen über die Fortpflanzung einiger Rhizopoden, Arb. a. d. k. Gsndtsamte, 1903, xix, 547.

4. Craig: Observations on Amebas Infecting the Human Intestine, with a Description of Two Species, *Entamoeba Coli* and *Entamoeba Dysenteriae*, Am. Med., 1905, ix, 854, 897.

pseudopodia of this species have the power to penetrate the cells of the intestinal mucosa. The nucleus of *Entamoeba histolytica* is difficult to find, being almost homogeneous with the protoplasm of the cell body; its nuclear membrane is but slightly refractile and there is only a single nucleolus surrounded by a narrow zone of chromatin. Multiplication is by simple fission or by spore formation through budding, making the resting stage.

The ipecac treatment of amebic colitis has had a varied history with its periods of ascendancy and decline. The method of administration suggested by one of the later advocates of this treatment merits analysis. The initial dose is 50 grains of powdered ipecac. This is reduced 5 grains each day, until 10 grains are reached. This amount is continued for two weeks. It is advised that the drug be given in pills, each containing 5 grains and each coated with  $\frac{1}{8}$  inch of phenyl salicylate (salol). Such a pill, the powdered ipecac being increased in bulk by 2 grains of the necessary excipient, would weigh about 37 grains, would have a diameter of  $\frac{9}{16}$  inch and contain about 30 grains of phenyl salicylate. To swallow ten such pills is no small feat, while the phenyl salicylate thus ingested would amount to about 300 grains. If the coating is made  $\frac{1}{16}$  inch, each pill would contain about 13 grains of phenyl salicylate and the total amount given with 10 pills, about 130 grains. This was enough to produce dark urine in the case here reported, and largely prevented absorption of the ipecac, since several pills were found in the stools with the coating only partially dissolved.

One is naturally led to question how far phenyl salicylate by its action as an intestinal antiseptic may have been a factor in the favorable results observed by some in this treatment and, further, if the failure to gain the characteristic effects of ipecac as an emetic may be owing to lack of absorption through protection by the covering phenyl salicylate. This supposition gains proof from the severe vomiting following the administration of the keratin-coated ipecac pills.

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# A STUDY OF THE DUODENAL CONTENTS IN MAN\*

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## INTRODUCTION

Formerly the only method of studying the secretion of the pancreas was by means of a temporary or permanent fistula. Lately one of us (Einhorn<sup>1</sup>) has described a practical method of obtaining the duodenal contents in man, which makes the duodenal contents accessible for analysis.

It appears to us of importance to investigate a few of the problems with regard to pancreatic secretion in man and to compare our results with those previously obtained by the methods mentioned above.

The present paper deals with the influence of various foods and drugs on the duodenal contents (bile, pancreatic secretion and duodenal juice) and also presents some data of chemical interest regarding the secretion. Attention was paid to the quantity of secretion obtained and to its different qualities.

## METHOD USED FOR OBTAINING THE SECRETION

Unless otherwise stated, the patient at each experiment in the fasting condition drank one cup of tea with sugar. Forty-five minutes later the duodenal pump was inserted. As soon as the latter had reached the duodenum, the article to be tested was given in a bulk of 150 c.c. and forty-five minutes later aspiration of the duodenal contents for fifteen minutes was performed.

The insertion of the pump is accomplished in the following manner:<sup>2</sup>

The capsule of the duodenal pump, as well as the lower part of the rubber tube, are moistened with warm water and put into the pharynx

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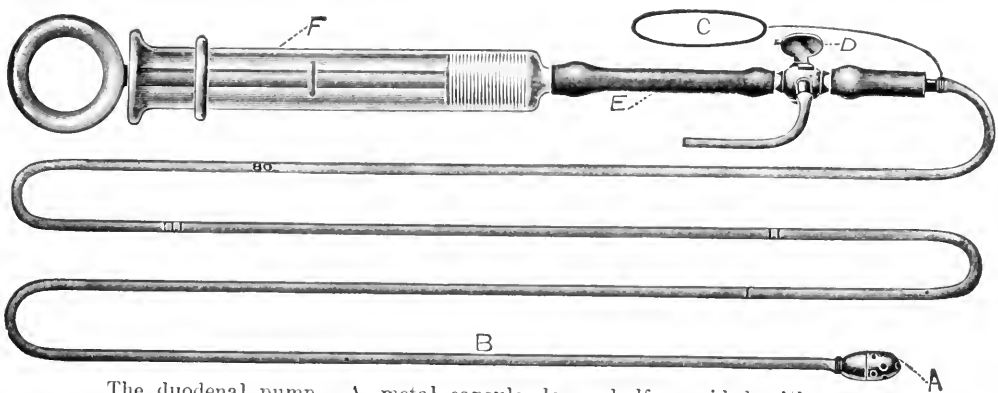
\* Some of the analytical work in this paper was carried out in the laboratory of Biological Chemistry of Columbia University at the College of Physicians and Surgeons, for which we desire to thank Professor W. J. Gies.

\* From the Chemical Division of the Pathologic Laboratory of the German Hospital in the City of New York.

1. Einhorn, Max: A Practical Method of Obtaining the Duodenal Contents in Man. *Med. Rec.*, 1910, lxxvii, 98.

2. For further details regarding the pump, see original article (Note 1).

of the patient. Then the latter drinks some water, and the instrument thus soon passes into the stomach. To be certain that the capsule has not become stuck in the esophagus, it is well to have the patient shake his abdomen and to aspirate a syringe-ful of chyme. This can easily be identified as gastric contents. Now a syringe-ful of water and then one of air are passed through the instrument. The rubber tube is then clamped off and left alone for about one hour. The patient is told not to close his mouth too tightly, so that the tube is not retarded in its wanderings. The patient must also avoid intentional swallowing of the tube. Through the peristalsis of the stomach the capsule is pushed on further, and usually passes through the pylorus into the duodenum and later into the beginning of the small intestine. It is best to have the patient read some light literature, in order to divert his attention. After one hour the distance that the capsule has progressed is examined: if sign III (see illustration)



The duodenal pump. A, metal capsule, lower half provided with numerous holes; the upper half communicating with tube B; I, II, III, marks of I=40, II=56, III=70 cm. from capsule; C, rubber band with silk attached to end of tubing, which can be placed over the ear of patient; F, aspirating syringe; E, collapsible connecting tube; D, three-way stopcock.

is near the lips (70 cm.) or inside the mouth, aspiration is attempted. If the capsule is in the duodenum, a clear, golden yellow or watery liquid of alkaline reaction and somewhat viscid consistency is generally obtained. If, however, the capsule is in the stomach, an acid liquid, resembling the one first removed is obtained.

#### METHOD FOR DETERMINING THE ENZYMES

*Amylase.*—To 10 c.c. of a 1 per cent. solution of freshly prepared starch paste was added 1 c.c. of the juice and 1 c.c. of toluol, and the mixture allowed to digest at 40 C. until duplicates showed no longer blue with

iodin solution. At this point the bottles containing the digestive mixture were placed in boiling water to stop digestion at the same moment. The contents were then made up to 50 c.c. and run in from a burette into boiling Fehling's solution, acetic acid and potassium ferrocyanid being used to determine the end point. The number of cubic centimeters of the digestive mixture required to reduce 10 c.c. Fehling's solution 0.05 gm. dextrose or its equivalent of maltose was ascertained. When the amount of sugar in the digestive mixture was less than that required to reduce the copper, a standard dextrose solution was added.

*Lipase.*—One c.c. of the juice, 10 c.c. of water, 1 c.c. of neutral ethyl butyrate and 1 c.c. toluol were placed in a bottle and allowed to digest at

TABLE 1.—THE DUODENAL CONTENTS IN THE FASTING CONDITION

Name.	Date.	Amount c.c.	Reaction.	Color.	Trans- parency.	Lipase * c.c.	Amylase † c.c.	Alkali-Pro- tease ‡ mm.	Diagnosis.
Mr. R.....	3/26	10	Neutral	Golden yellow	Cloudy	3.9	37.7	5	Neurotic vomiting.
Mr. U.....	4/ 7	5	Neutral	Golden yellow	Clear	2.4	46	3	Chronic gastritis.
Mr. U.....	4/ 9	2	Neutral	Golden yellow	Clear	2.4	**	0	Chronic gastritis.
Miss S.....	4/16	25	Neutral	Golden yellow	Clear	12.0	36	5	Gastric ulcer.
Mr. H.....	3/ 4	12	Neutral	Golden yellow	Clear	0.9	49.2	1	Banti's disease.
Mr. H.....	3/ 5	15	Neutral	Golden yellow	Clear	0.7	48.6	1	Banti's disease.
Mr. H.....	3/26	25	Neutral	Golden yellow	Clear	4.6	36.5	3	Banti's disease.
Mr. H.....	4/16	40	Neutral	Golden yellow	Cloudy	2.8	50	2	Banti's disease.
Mr. H.....	4/18	20	Neutral	Golden yellow	Cloudy	2.0	39	2	Banti's disease.

\* Lipase values are given in the amount of 1/20 normal solution of sodium hydroxid necessary to neutralize the acidity developed.

\*\* 50 ÷ 0.03 glucose.

† Amylase values are given in the number of cubic centimeters of the digestive mixture, which, when made up to 50 c.c., were equivalent to 0.05 gm. of glucose.

‡ Alkali-protease (trypsin) values are given in the number of millimeters of gelatin digested.

40 C. After twenty-four hours one-twentieth normal solution of sodium hydroxid in water, with phenolphthalein as an indicator, was used to determine the amount of acidity developed. From this amount was subtracted the amount of acidity, if any, in the duplicates containing 1 c.c. of juice plus 10 c.c. water and 1 c.c. toluol. Each digestive mixture was shaken ten times during the twenty-four hours.

*Alkali-Protease (Trypsin).*—Preparation of Gelatin Tubes: Ten gm. of gelatin were dissolved in 100 c.c. of a 1 per cent. solution of sodium fluorid and colored with methyl violet. This solution was drawn up into



TABLE 2.—THE EFFECT OF SECRETIN ON THE DUODENAL CONTENTS

Name	Date	Amount c.c.	Reaction	Color	Trans- parency	Lipase, c.c.	Amyl- lopsin, c.c.	Alkal- phosph., mm.	Diagnosis	Remarks
Mr. U.	4/7	5	Neutral	Golden yellow	Cloudy	2.4	46	3	Chronic gastritis.	Fasting.
Mr. U.	4/7	8	Neutral	Golden yellow	Cloudy	5.6	47	3	Chronic gastritis	One and one-quarter hrs. after tea and sugar.
Mr. U.	4/7	30	Neutral	Golden yellow	Clear	4.4	50	5	Chronic gastritis	After secretin* by mouth.
Mr. U.	4/9	2	Neutral	Golden yellow	Clear	2.4	55	0	Chronic gastritis	Fasting.
Mr. U.	4/9	10	Neutral	Golden yellow	Clear	3.2	50	4	Chronic gastritis	After secretin by mouth.
Mr. S.	3/30	30	Neutral	Golden yellow	Cloudy	6.8	36	3	Chronic append- icitis	After secretin by mouth.
Mr. S.	4/1	17	Neutral	Golden yellow	Cloudy	4.1	38	6	Chronic append- icitis	After secretin by mouth.
Mr. S.	4/2	13	Neutral	Golden yellow	Clear	9.6	45	3	Chronic append- icitis	After water.
Mr. S.	4/2	35	Neutral	Golden yellow	Clear	9.2	50	6	Chronic append- icitis	After secretin by hypo.
Mr. H.	3/30	40	Neutral	Golden yellow	Clear	4.1	28	8	Bant's disease	After secretin by mouth.
Mr. H.	4/1	30	Neutral	Golden yellow	Clear	7.9	40	3	Bant's disease	After secretin by mouth.
Mr. H.	4/2	35	Neutral	Golden yellow	Clear	7.6	48	3	Bant's disease	After water.
Mr. H.	4/2	50	Neutral	Golden yellow	Clear	7.2	50	5	Bant's disease	After secretin by hypo.
Mr. H.	4/4	90	Neutral	Golden yellow	Clear	1.2	48	2	Bant's disease	Before secretin.
Mr. H.	4/4	35	Neutral	Golden yellow	Clear	3.2	50	3	Bant's disease	After secretin by mouth.
Mr. H.	4/5	32	Neutral	Golden yellow	Clear	4.0	50	6	Bant's disease	After secretin by mouth.
Mr. H.	4/9	27	Neutral	Golden yellow	Clear	2.8	49	2	Bant's disease	Before secretin by mouth
Mr. H.	4/9	19	Neutral	Golden yellow	Clear	3.6	47	4	Bant's disease	After secretin by mouth
Mr. H.	4/9	8	Neutral	Golden yellow	Clear	2.0	35	3	Bant's disease	Before secretin by mouth.
Mr. H.	4/9	30	Neutral	Golden yellow	Clear	4.0	35	5	Bant's disease	After secretin, 15 min after siphonage.
Mr. H.	4/26	55	Neutral	Golden yellow	Clear	3.2	51	2	Bant's disease	After above 5 ml. adre- nalin intravenously.

\* A preparation made by Fairchild Bros. and Foster.

\*\* 50 U 0.03 glucose.

TABLE 3.—THE EFFECT OF VARIOUS NUTRITIVE FLUIDS ON THE DUODENAL CONTENTS \*

Name.	Date.	Amount c.c.	Reaction.	Color.	Trans- parency.	Lipase, c.c.	Amylase, c.c.	Alkali- phosphate, mm.	Diagnosis.	Remarks.
Mr. L.....	3/2	10	Neutral	Golden yellow	Cloudy	0.9	49.8	4	Gastric atony and dilatation	Before bouillon.
Mr. L.....	3/2	21	Neutral	Golden yellow	Clear	3.8	34.7	4	Gastric atony and dilatation	After bouillon.
Mr. L.....	3/2	6	Neutral	Golden yellow	Clear	4.7	31.4	6	Gastric atony and dilatation	One hour and 45 minutes after bouillon.
Mr. L.....	3/2	12	Neutral	Golden yellow	Clear	4.2	33.1	5	Gastric atony and dilatation	After tea and milk.
Mr. W.....	3/4	10	Neutral	Golden yellow	Clear	0.1	0	0	Gastric neurosis	Before bouillon.
Mr. W.....	3/4	3	Neutral	Golden yellow	Clear	0.2	0	0	Gastric neurosis	After bouillon.
Mr. W.....	3/5	5	Neutral	Golden yellow	Clear	0.1	0	0	Gastric neurosis	Before bouillon.
Mr. W.....	3/5	15	Neutral	Golden yellow	Clear	4.9	37.2	4	Gastric neurosis	After bouillon.
Mr. M.....	3/4	5	Neutral	Golden yellow	Clear	4.2	48.7	3	Gastric ulcer and pulmonary	After bouillon.
Mr. M.....	3/4	22	Neutral	Golden yellow	Clear	5.6	36.2	5	Gastric ulcer and pulmonary	One hour and 45 minutes after bouillon.
Mr. L.....	3/5	8	Neutral	Golden yellow	Clear	0.2	49.4	2	Chronic gastritis	Before bouillon.
Mr. L.....	3/5	35	Neutral	Golden yellow	Clear	5.1	34.8	5	Chronic gastritis	After bouillon.
Mr. S.....	3/25	17	Neutral	Golden yellow	Clear	4.2	35.0	4	Chronic appendicitis and gastritis	After bouillon.
Mr. May.....	3/19	8	Acid	Golden yellow	Cloudy	0.2	0	0	Carcinoma of liver	Thirty minutes after tea and sugar.
Mr. May.....	3/19	4	Acid	Golden yellow	Cloudy	0.3	0	0	Carcinoma of liver	Forty-five minutes after tea and sugar.
Mr. May.....	3/19	10	Acid	Golden yellow	Cloudy	5.2	39.3	4	Carcinoma of liver	One hour after tea and sugar.
Mr. May.....	4/4	45	Acid	Golden yellow	Clear	5.6	35.0	3	Carcinoma of liver	After bouillon.
Mr. V.....	4/7	5	Neutral	Golden yellow	Clear	2.4	46.0	3	Carcinoma of liver	Fasting.
Mr. V.....	4/7	8	Neutral	Golden yellow	Clear	5.6	47.0	3	Carcinoma of liver	One hour and 15 minutes after tea and sugar.
Mr. H.....	3/1	5	Neutral	Golden yellow	Clear	2.8	40.1	2	Banti's disease	One-half hour after tea and milk.
Mr. H.....	3/1	6	Neutral	Golden yellow	Clear	4.0	38.1	2	Banti's disease	Two hours after tea and milk.
Mr. H.....	3/1	8	Neutral	Golden yellow	Clear	4.2	39.2	3	Banti's disease	After bouillon.
Mr. H.....	3/1	21	Neutral	Golden yellow	Clear	6.8	30.2	4	Banti's disease	One hour after bouillon.
Mr. H.....	3/19	25	Acid	Golden yellow	Clear	7.1	32.1	6	Banti's disease	Two and one-quarter hours after bouillon.
Mr. H.....	4/27	25	Neutral	Golden yellow	Clear	3.2	35.0	5	Banti's disease	Forty-five minutes after water.
Mr. H.....	4/2	35	Neutral	Golden yellow	Clear	7.6	48.0	3	Banti's disease	After water.
Mr. S.....	4/2	13	Neutral	Golden yellow	Clear	9.6	45.0	3	Chronic appendicitis	After water.

\* Throughout our experiments with various nutritive fluids, 150 c.c. of the fluid to be tested was given.

TABLE 4. EFFECT OF BOULLON AND HYDROCHLORIC ACID ON THE DUODENAL CONTENTS

Name.	Date.	Amount c.c.	Reaction.	Color.	Trans- parency.	Lipase, c.c.	Amylase, c.c.	Alkali- Phosphate, mm.	Diagnosis.	Remarks.
Mr. L. ....	3/2	4	Neutral	Golden yellow	Clear	0.9	49.8	1	Gastric atony and dilatation	Before bouillon and hydrochloric acid.
Mr. L. ....	3/2	20	Acid	Golden yellow	Clear	3.2	55.8	4	Gastric atony and dilatation	After bouillon and m. xv hydrochloric acid.
Mr. R. ....	3/25	22	Acid	Golden yellow	Clear	5.1	37.3	5	Neurotic vomiting	After m. xv hydrochloric acid.
Mr. H. ....	3/14	60	Neutral	Golden yellow	Clear	7.0	31.1	5	Bant's disease	After bouillon and m. xv hydrochloric acid.
Mr. H. ....	3/25	45	Neutral	Golden yellow	Clear	6.9	33.2	7	Bant's disease	One hour and 15 minutes after m. xv hydrochloric acid.

TABLE 5. EFFECT OF BOULLON AND SODIUM BICARBONATE ON THE DUODENAL CONTENTS

Name.	Date.	Amount c.c.	Reaction.	Color.	Trans- parency.	Lipase, c.c.	Amylase, c.c.	Alkali- Phosphate, mm.	Diagnosis.	Remarks.
Mr. S. ....	3/27	20	Neutral	Golden yellow	Clear	4.5	31.5	5	Chronic appendicitis	After bouillon and sodium bicarbonate.
Mr. R. ....	3/27	11	Neutral	Golden yellow	Clear	4.5	11.0	1	Neurotic vomiting	After bouillon and sodium bicarbonate.
Mr. H. ....	3/27	52	Acid	Golden yellow	Clear	8.0	36.0	5	Bant's disease	After bouillon and sodium bicarbonate.

TABLE 6. EFFECT OF WATER AND BRANDY ON THE DUODENAL CONTENTS

Name.	Date.	Amount c.c.	Reaction.	Color.	Trans- parency.	Lipase, c.c.	Amylase, c.c.	Alkali- Phosphate, mm.	Diagnosis.	Remarks.
Mr. S. ....	3/29	24	Neutral	Golden yellow	Clear	2	28.5	3	Chronic appendicitis	After water and brandy.
Mr. S. ....	3/31	21	Neutral	Golden yellow	Clear	4	50.0	1	Chronic appendicitis	After water and brandy.
Mr. H. ....	3/29	12	Acid	Golden yellow	Clear	3.6	11.0	5	Bant's disease	After water and brandy.
Mr. H. ....	3/31	45	Neutral	Golden yellow	Clear	6.0	40.0	3	Bant's disease	After water and brandy.

TABLE 7.—EFFECT OF BOUILLON AND ATROPIN ON THE DUODENAL CONTENTS

Name.	Date.	Amount c.c.	Reaction.	Color.	Trans- parency.	Lipase. c.c.	Amylase. c.c.	Alkali- Protease. mm.	Diagnosis.	Remarks.
Mr. S.....	3/26	15	Neutral	Golden yellow	Clear	4.0	37.0	4	Appendicitis	After bouillon and nux vomica.
Mr. M.....	3/21	20	Acid	Golden yellow	Clear	4.1	43.2	3	Carcinoma of liver	After bouillon and gr. 1/120 atropin.
Mr. M.....	4/5	25	Acid	Golden yellow	Clear	4.2	40.0	4	Carcinoma of liver	One hour and 30 minutes after bouillon and gr. 1/120 atropin.
Mr. H.....	3/15	70	Neutral	Golden yellow	Clear	3	33.2	4	Banti's disease	After atropin.
Mr. H.....	3/22	45	Acid	Golden yellow	Clear	4	30.0	3	Banti's disease	After atropin.
Mr. H.....	4/16	43	Neutral	Golden yellow	Clear	4.4	46.0	3	Banti's disease	After atropin.

TABLE 8.—EFFECT OF PILOCARPIN AND OTHER SUBSTANCES ON THE DUODENAL CONTENTS

Name	Date.	Amount c.c.	Reaction.	Color.	Trans- parency	Lipase. c.c.	Amy- lase. c.c.	Alkali- Protease. mm.	Diagnosis.	Remarks.
Mr. H.....	3/16	50	Neutral	Golden yellow	Clear	5.0	36.2	3	Banti's disease	After bouillon and gr. 1/2 pilocarpin.
Mr. H.....	3/24	45	Acid	Golden yellow	Clear	5.0	36.1	4	Banti's disease	After bouillon and gr. 1/2 pilocarpin.
Mr. H.....	4/18	45	Neutral	Golden yellow	Clear	2.8	49.0	4	Banti's disease	After bouillon and gr. 1/2 pilocarpin.
Miss S.....	4/27	100	Neutral	Golden yellow	Clear	4.4	30.0	6	Gastric ulcer	Aspirated for 1 hour after feeding through tube.
Mr. H.....	4/7	30	Neutral	Golden yellow	Clear	2.8	50.0	6	Banti's disease	After Magendie solution, m. v.
Mr. H.....	4/7	31	Neutral	Golden yellow	Clear	6.4	48.0	4	Banti's disease	After olive oil, 1 dram.
Mr. H.....	4/8	20	Neutral	Golden yellow	Clear	2.4	50.0	5	Banti's disease	After gr. 2 eafamel.
Mr. H.....	4/11	55	Neutral	Golden yellow	Clear	3.6	50.0	3	Banti's disease	After podophyllin, 0.01 gm.
Mr. H.....	4/12	40	Neutral	Golden yellow	Clear	2.4	49.0	6	Banti's disease	After podophyllin, 0.01 gm.
Mr. H.....	4/15	80	Acid	Golden yellow	Clear	2.8	49.5	1	Banti's disease	After glucose.
Mr. H.....	4/20	28	Neutral	Golden yellow	Clear	3.2	40.0	5	Banti's disease	After holadin*
Mr. H.....	4/22	42	Neutral	Golden yellow	Clear	3.2	31.6	5	Banti's disease	After holadin.*
Mr. H.....	4/23	27	Neutral	Golden yellow	Clear	2.4	31.0	9	Banti's disease	After holadin.*

\* Holadin (Fairchild Bros. and Foster), supposed to contain the enzymes of the pancreas, each capsule containing  $2\frac{1}{2}$  gr. holadin and  $\frac{1}{2}$  gr. bile salts.

TABLE 9.—INVESTIGATIONS ON PATIENT WITH HYPERTROPHIC CIRRHOSIS OF LIVER

Date.	Amount c.c.	Reaction.	Color.	Trans- par- ency.	Lipase c.c.	Amy- lase, c.c.	Alkali- Protease, mm.	Remarks.
3/ 1	21	Neutral	Golden yellow	Clear	6.8	39.2	4	Two hours and 15 minutes after bouillon.
3/ 1	6	Neutral	Golden yellow	Clear	4.0	38.1	2	Two hours after tea and milk.
3/ 1	5	Neutral	Golden yellow	Clear	2.8	40.1	2	One-half hour after tea and milk.
3/ 1	8	Neutral	Golden yellow	Clear	4.2	39.2	3	After bouillon.
3/ 4	12	Neutral	Golden yellow	Clear	0.9	49.2	1	Before milk (1 hour).
3/ 4	15	Neutral	Golden yellow	Clear	0.7	48.6	1	Before milk (45 minutes).
3/14	60	Neutral	Golden yellow	Clear	7.0	34.1	5	After bouillon and xv m. HCl.
3/15	70	Neutral	Golden yellow	Clear	3.0	33.2	4	One hour and 20 minutes after bouillon and gr. 1/120 atropin.
3/16	50	Neutral	Golden yellow	Clear	5.0	36.2	3	After bouillon and pilocarpin, 1/12 gr.
3/19	26	Neutral	Golden yellow	Clear	7.1	32.1	6	One hour after bouillon, aspirated for 10 minutes.
3/22	45	Neutral	Golden yellow	Clear	4.0	30.0	3	After bouillon and atropin, gr. 1/120.
3/24	45	Neutral	Golden yellow	Clear	5.0	36.1	4	After bouillon and pilocarpin, gr. 1/12.
3/25	45	Acid	Golden yellow	Clear	6.0	33.2	7	One hour and 15 minutes after bouillon and m. xv HCl.
3/26	25	Neutral	Golden yellow	Clear	4.6	36.5	3	After bouillon.
3/27	52	Acid	Golden yellow	Clear	8.0	36.0	5	After bouillon and sodium bicarbonate, 1 dram.
3/29	42	Acid	Golden yellow	Clear	3.6	44.0	5	After water and brandy.
3/30	40	Neutral	Golden yellow	Clear	4.4	28.0	8	After secretin by mouth.
3/31	45	Neutral	Golden yellow	Clear	6.0	40.0	3	After water and brandy.
4/ 1	30	Neutral	Golden yellow	Clear	7.2	40.0	3	After secretin by mouth.
4/ 2	35	Neutral	Golden yellow	Clear	7.6	48.0	3	After water.
4/ 2	50	Neutral	Golden yellow	Clear	7.2	50.0	5	After secretin by hypo.
4/ 4	20	Neutral	Golden yellow	Clear	1.2	50.0	2	Before secretin.
4/ 4	35	Neutral	Golden yellow	Clear	3.2	48.0	3	After secretin by mouth.
4/ 5	32	Neutral	Golden yellow	Clear	4.0	50.0	6	After secretin by mouth.
4/ 7	30	Neutral	Golden yellow	Clear	2.8	50.0	5	After Magendie solution.
4/ 7	31	Neutral	Golden yellow	Clear	6.4	48.0	4	After olive oil.
4/ 8	20	Neutral	Golden yellow	Clear	2.4	50.0	5	After calomel, gr. 2.
4/ 9	27	Neutral	Golden yellow	Clear	3.6	47.0	4	Before secretin.
4/ 9	19	Neutral	Golden yellow	Clear	2.8	42.0	2	After secretin by mouth.
4/11	55	Neutral	Golden yellow	Clear	3.6	50.0	3	After podophyllin.
4/12	20	Neutral	Golden yellow	Clear	2.4	50.0	6	After podophyllin.
4/15	80	Acid	Golden yellow	Clear	2.8	50.0	1	After glucose.
4/16	40	Neutral	Golden yellow	Clear	2.8	50.0	9	Fasting.
4/16	43	Neutral	Golden yellow	Clear	4.4	46.0	3	Forty-five minutes after atropin.
4/18	20	Neutral	Golden yellow	Clear	2.0	39.0	2	Fasting.

TABLE 9.—(Continued)

Date.	Amount c.c.	Reaction.	Color.	Trans- par- ency.	Lipase c.c.	Amy- lase, c.c.	Alkali- Protease, mm.	Remarks.
4/18	45	Neutral	Golden yellow	Clear	2.8	49.0	4	After pilocarpin (gr. 1/12).
4/20	28	Neutral	Golden yellow	Clear	3.2	40.0	5	After holadin.
4/22	42	Neutral	Golden yellow	Clear	3.2	31.0	8	After holadin.
4/23	27	Neutral	Golden yellow	Clear	2.4	31.0	9	After holadin.
4/26	8	Neutral	Golden yellow	Clear	2.0	35.0	5	Before secretin.
4/26	30	Neutral	Golden yellow	Clear	1.0	35.0	5	After secretin (siphonage).
4/26	55	Alkaline	Golden yellow	Clear	3.2	50.0	2	After above m. v adrenalin given intravenously.
4/27	25	Neutral	Golden yellow	Clear	3.2	35.0	5	Forty-five minutes after water (siphonage).

capillary tubing 1 mm. in diameter, and the tubing quickly placed under cold water to congeal the gelatin solution. The tubing was then cut up into lengths of 2 cm.

Determination of Alkali-Protease: Ten c.c. of the juice were placed in a small bottle, closed with a perforated cork through which the gelatin tubes could be inserted. The digestions were kept at room temperature for forty-eight hours to determine the alkali-protease. One c.c. of toluol was added to each digestive mixture and enough 0.2 per cent. sodium carbonate solution to make the mixture alkaline in reaction.<sup>3</sup>

The results in Table 1 show that the duodenum in the fasting condition contains an active digestive fluid; that is, under the conditions stated, when the duodenal pump is in the digestive tract.

The results in Table 2 show that secretin given by mouth or hypodermically usually produces a more active digestive secretion and always a greater amount of fluid.

The administration of bouillon produced a more abundant and active digestive fluid, as also did water, but tea with milk or sugar did not cause any marked change in the character of the secretion (Table 3).

It can be seen from Table 4 that after the administration of bouillon and hydrochloric acid the juice was more abundant and more active.

The administration of bouillon and sodium bicarbonate stimulated the secretion, both as to quantity and activity (Table 5).

3. In almost all of the digestion experiments duplicates were made with the boiled secretion and the results, if any, subtracted from that obtained with the unboiled secretion.

Water and brandy stimulated the secretion, especially in regard to the quantity obtained (Table 6).

Bouillon and atropin produced an abundant secretion of somewhat poorer quality (Table 7).

The administration of pilocarpin caused a more abundant secretion and also a more active fluid (Table 8). There was not much change in the character of the fluid after administration of Magendie solution, olive oil, calomel or podophyllin, with exception of a small increase in the amount.

Glucose produced a more abundant secretion of juice but of poor digestive ability, especially as regards trypsin. Holadin caused a more abundant secretion of a very active juice.

In one patient (with hypertrophic cirrhosis of the liver), who, besides, gave a positive Cammidge reaction, we were fortunate enough to undertake various and numerous investigations, which we consider worth while to compile (Table 9). This table shows very clearly the marked variations in the character of the secretion obtained under the same conditions, but after the administration of various substances.

#### SOME CHEMICAL DATA REGARDING THE DUODENAL CONTENTS<sup>4</sup>

The contents as obtained were viscid, nearly always clear and with a strong bile color. The contents frothed readily on shaking and contained coagulable protein, protease and peptone. The reaction usually was neutral to litmus, phenolphthalein, lacmoid, alizarin, cochineal and rose-olic acid, seldom alkaline or acid.

Following are some quantitative results obtained on analysis of the duodenal contents:

Parts per 1,000.	1. Secretion after fasting.	2. Secretion after duodenal tube feeding.*
Total solids .....	14.40	14.10
Organic matter .....	10.27	10.08
Ash .....	4.13	4.02
Coagulable protein ....	1.42	1.22
Total nitrogen .....	0.924	0.785
Specific gravity .....	1.005	1.004

\* An hour and three quarters after last feeding.

#### SUMMARY

In this paper we have corroborated the findings of physiologists in regard to the influence of various agents on the pancreatic secretion, with

4. The contents used for these analyses were obtained from a patient suffering from gastric ulcer who was fed through the duodenal pump for a period of two weeks.

the exception of the influence of sodium bicarbonate. We obtained evidence that it has a stimulating effect, instead of an inhibitory action.

It is our intention to continue this work, paying special attention to the character of the duodenal contents in various diseases in which we might expect some change in the nature of the duodenal secretions.

In conclusion we desire to thank Prof. W. G. MacCallum for his interest and cooperation and Drs. Hoff and Steinbugler for their valuable assistance.

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## A STUDY OF HUMAN AND ANIMAL TYPHOID AGGLUTININS \*

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With the increasing interest in prophylactic typhoid vaccine inoculations, the question frequently arises as to what is the best method of judging the protective power created in the serum of the vaccinated individual. It has been claimed by Leishman<sup>1</sup> that there is a certain relation between the appearance of the agglutinating and the bactericidal power in the serum of vaccinated individuals. Therefore, the agglutinating power of a serum is probably some indication of its protective power. The work on which this paper is based has consisted of the study of the agglutinating power in the serum of typhoid fever patients, the development of typhoid agglutinins in rabbits' serums, and the effect of their serums on that of other rabbits.

In Osler's "Modern Medicine," it is stated that almost all cases of typhoid fever sooner or later develop in their serum the power to agglutinate the *Bacillus typhosus* at a dilution of 1 to 50. Stone,<sup>2</sup> in 1909, reports that in the second week of the disease the serum of patients will give a positive agglutination reaction at a dilution of 1 to 100, and with the decline of the fever at a dilution of 1 to 60 or 1 to 80, and that it is rare to obtain a positive reaction with dilutions of 1 to 400 and very rare at 1 to 1,000. Leishman<sup>3</sup> and Harrison found a positive reaction in a case six months after the beginning of the illness with a dilution of 1 to 1,000.

In this work fifty specimens of serum were collected from thirteen patients at different periods of the disease. The serums were examined on the same day or subsequent days. They were kept at a temperature

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\* From the laboratory of the Department of Theory and Practice of Physic, Harvard University, Boston, Mass.

\* Published with the approval of the committee as part of the work done under a Bullard Fellowship, Harvard University, 1909-10.

1. Leishman: Jour. Roy. Army Med. Corps, London, 1905, v. 1.

2. Stone, W. G.: Typhoid Immunity and Antityphoid Inoculation, Jour. Am. Med. Assn., 1909, liii, 1253.

3. Leishman and Harrison: Jour. Roy. Army Med. Corps, London, 1908, xi, 327.

just above 0 C., when not being used. It was shown that the agglutinating power of human serum, when kept at this temperature, remained the same for many days. A rabbit's serum kept at this temperature still had the same agglutinating power after eight months. The agglutination tests were made by the microscopic method on the hanging-drop slide. The serum was always diluted in a blood-counter pipette in order to minimize the source of error at that point. Actively motile bouillon cultures six to twenty-four hours old, transplanted from agar, were used. A drop of the culture and of the diluent (salt solution) were mixed on the cover-glass as a control, and no results were counted in which there was even moderate clumping in the control. A time limit of one hour was set for all dilutions. Only those reactions were called positive which fell under one of the following groups: those tests in which there was marked clumping that could easily be seen by the low power, even if there were still a few motile bacilli left; and those tests in which there was considerable clumping, but not in such large masses as the former group, provided that motion had ceased in all bacilli.

The charts of the thirteen patients are presented herewith. They simply show the course of the fever, the day of the disease, and the highest point of dilution at which the serum gave a positive agglutination test on the days it was collected.

From a study of these charts the following points of interest are brought out:

During the first week of the disease one serum was tested in the case of a patient who recovered without relapse. It was negative at a dilution of 1 to 10.

During the second week of the disease three serums were examined. These three from one patient who recovered without relapse, taken on different days of the week, gave positive tests at a dilution of 1 to 150 and negative tests at a dilution of 1 to 200. Thus the average highest dilution which gave a positive Widal test for this week was 1 to 150.

In the third week thirteen serums were tested. The highest dilution, 1 to 500, which gave a positive reaction occurred in the serum of a patient who recovered without relapse. The serums from a mild case without relapse were both negative at 1 to 10. Later this serum gave a positive test at a dilution of 1 to 100. One serum from a case which eventually terminated fatally was also negative at 1 to 10 dilution. This serum later developed an agglutinating power at a 1 to 100 dilution. The average highest dilution which gave a positive Widal test during this week was 1 to 155.

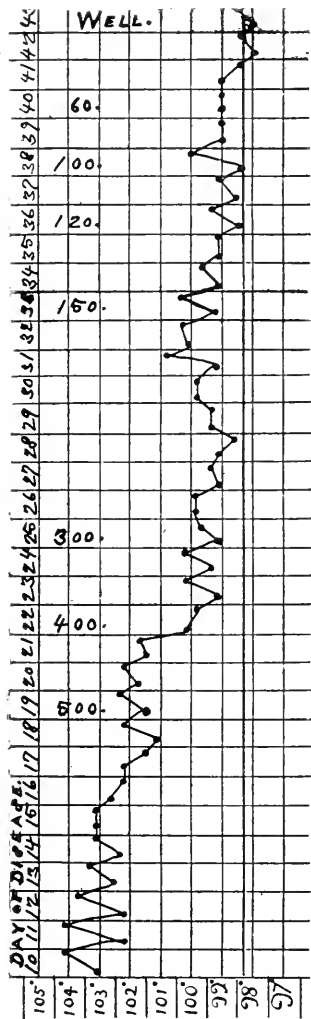


Chart 1.—Course of fever, day of disease, and highest point of dilution at which serum gave a positive agglutination test on the day collected.

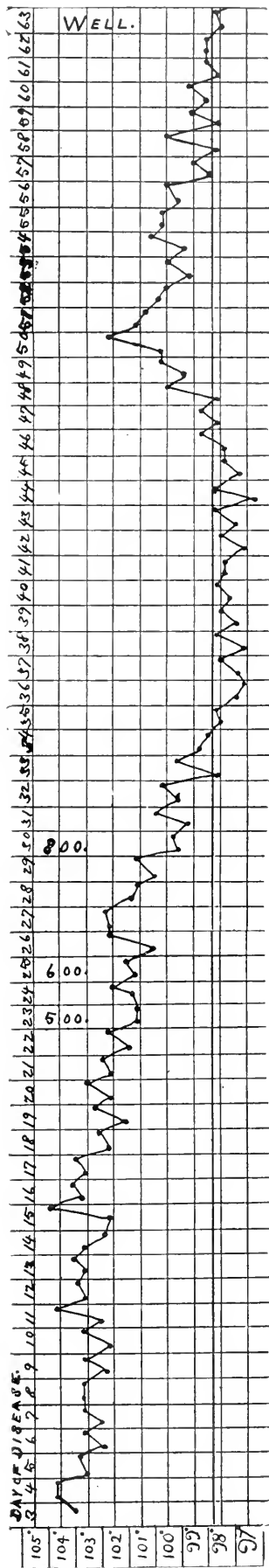


Chart 2.—Course of fever, day of disease, and highest point of dilution at which serum gave a positive agglutination test on the day collected.

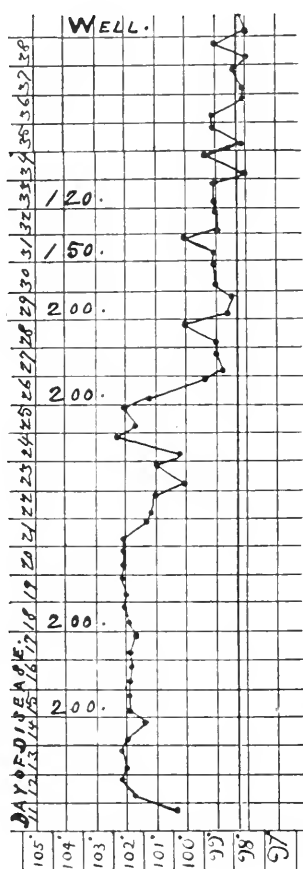


Chart 3.—Course of fever, day of disease, and highest point of dilution at which serum gave a positive agglutination test on the day collected.

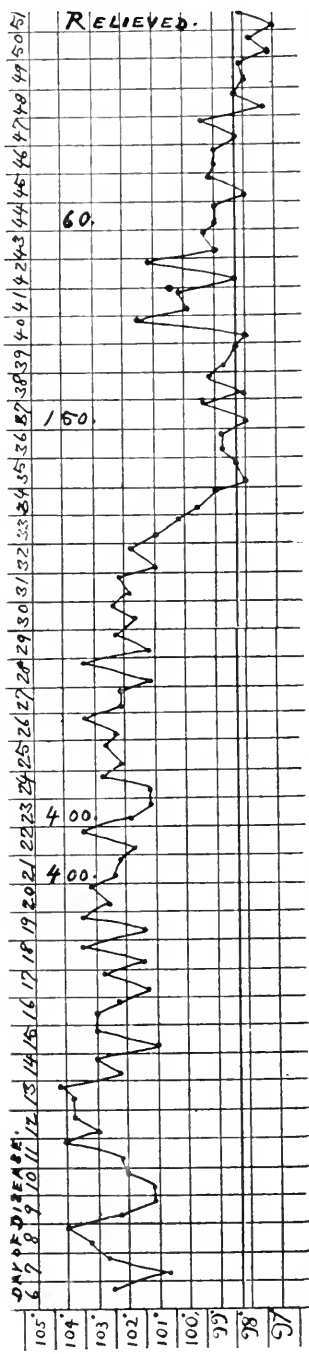


Chart 4.—Course of fever, day of disease, and highest point of dilution at which serum gave a positive agglutination test on the day collected.

In the fourth week fifteen serums were tested. The highest positive dilution, 1 to 600, occurred in the serum from a patient who eventually recovered after a relapse. There were no negative tests. The six tests positive only at a dilution of 1 to 100 were from the serums of three patients, one of whom recovered and two died. The average highest dilution for this week of the disease was 1 to 236.

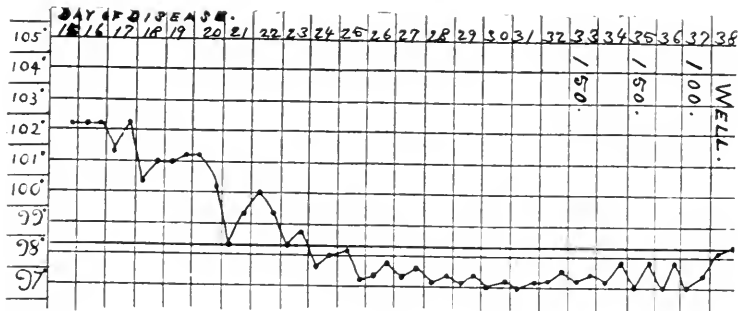


Chart 5.—Course of fever, day of disease, and highest point of dilution at which serum gave a positive agglutination test on the day collected.

Nine serums were tested from cases in the fifth week. One serum from a patient who eventually recovered after a relapse was positive at a dilution of 1 to 800. None of these serums gave negative tests. Of the two that gave a positive test only at a dilution of 1 to 120, one was from a case which terminated fatally, following a subsequent relapse. The average high point for this week was a dilution of 1 to 221.

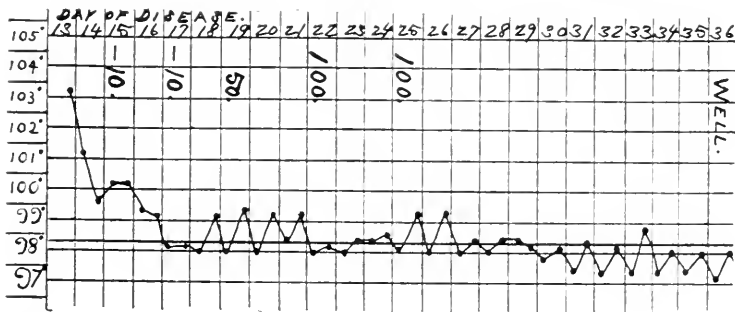


Chart 6.—Course of fever, day of disease, and highest point of dilution at which serum gave a positive agglutination test on the day collected.

Five serums were examined in the sixth week and showed as the limits of dilution at which positive tests were obtained 1 to 150 and 1 to 60. The average was 1 to 106. In the seventh week the limits in

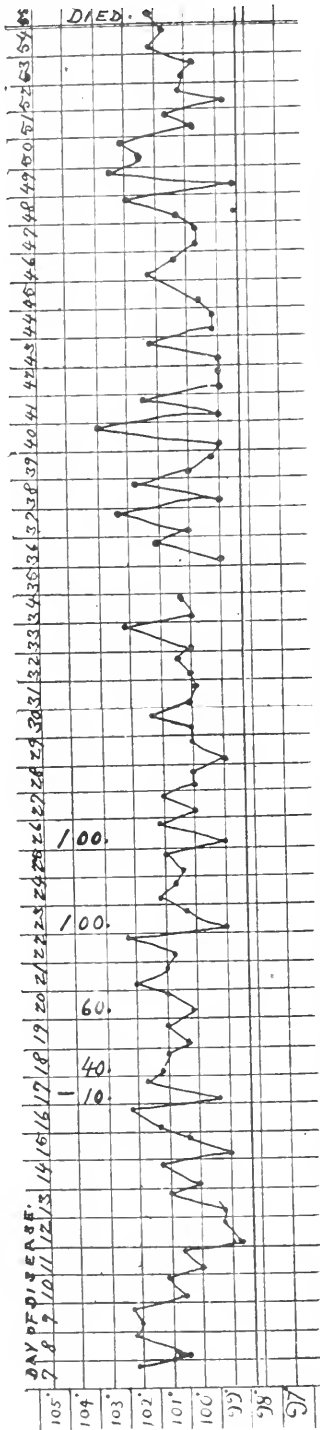


Chart 7. Course of fever, day of disease, and highest point of dilution at which serum gave a positive agglutination test on the day collected.

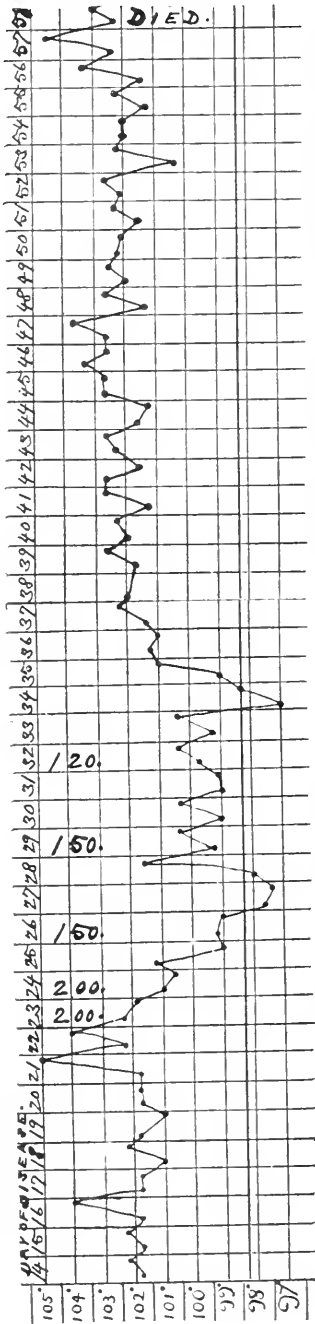


Chart 8.—Course of fever, day of disease, and highest point of dilution at which serum gave a positive agglutination test on the day collected.

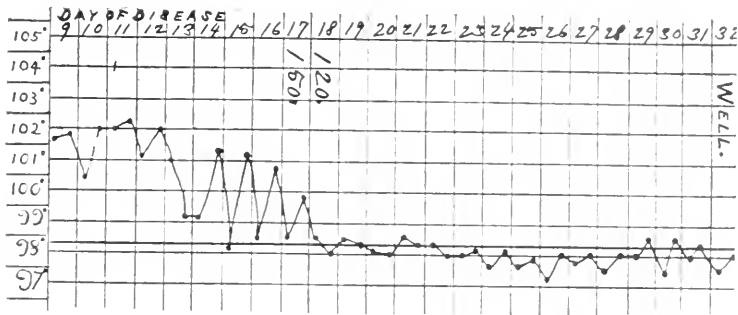


Chart 9.—Course of fever, day of disease, and highest point of dilution at which serum gave a positive agglutination test on the day collected.

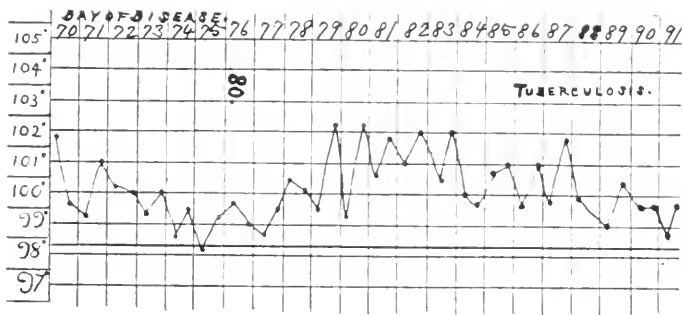


Chart 10.—Course of fever, day of disease, and highest point of dilution at which serum gave a positive agglutination test on the day collected.

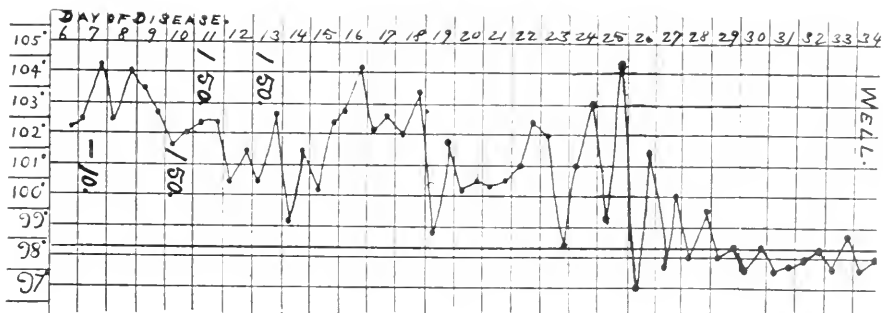


Chart 11.—Course of fever, day of disease, and highest point of dilution at which serum gave a positive agglutination test on the day collected.

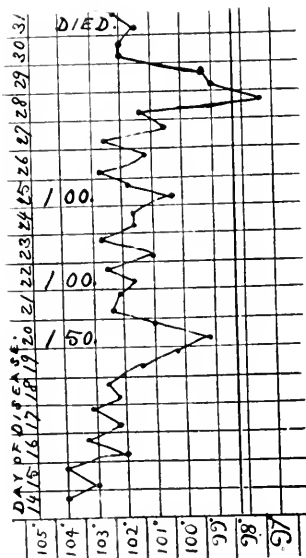


Chart 12.—Course of fever, day of disease, and highest point of dilution at which serum gave a positive agglutination test on the day collected.

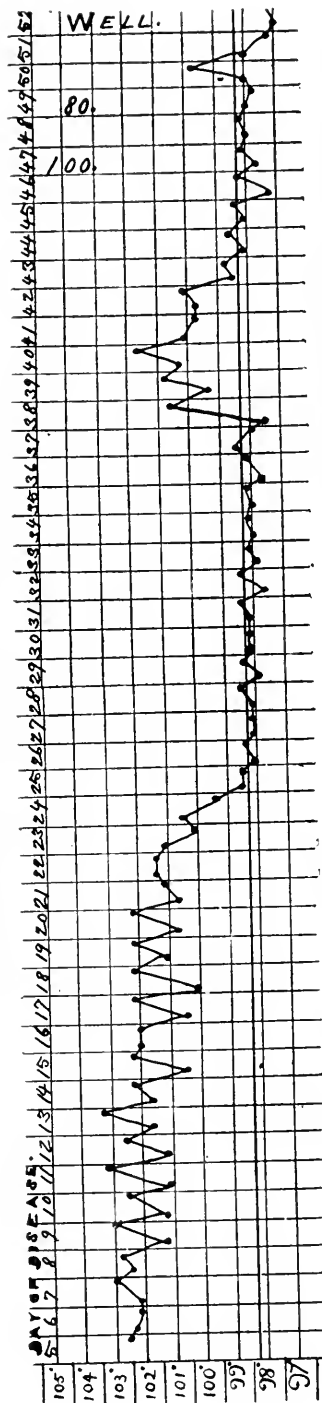


Chart 13.—Course of fever, day of disease, and highest point of dilution at which serum gave a positive agglutination test on the day collected.



three serums were 1 to 100 and 1 to 60 with an average of 1 to 80. In the eleventh week a patient who recovered without relapse showed a positive reaction at 1 to 80.

From a review of these results it appears that the agglutinating power reaches its height at the third and fourth weeks of the disease. Although individual cases may show an agglutinating strength capable of giving a positive reaction at a dilution of 1 to 800, the average highest dilution which will give a positive reaction at this period of the disease is about 1 to 225. In the three cases of the series which terminated fatally the highest dilution of the serum which would give a positive reaction was 1 to 200, and the average highest dilution of all the serums from the fatal cases that would give a positive reaction was 1 to 110.

The antityphoid serum used for the study of agglutinins was obtained by injecting at first dead, then live cultures of typhoid bacilli intraperitoneally into rabbits. This method produces a bacteriolytic serum with high agglutinating properties. No attempt was made to obtain the serum with the highest possible agglutinating power, and it is possible that other antisera such as Lüdke's<sup>4</sup> antiendotoxic serum may contain agglutinins more readily produced than the method herein employed.

A stock culture of the typhoid bacillus was used, which had lost considerable of its virulence. Six c.c. of a twenty-four-hour bouillon culture injected intraperitoneally would kill a rabbit of about 2,000 gm. weight. Of this stock culture, bouillon subcultures, six to twenty-four hours old, were used for injection. First a few cubic centimeters of the boiled culture were injected intraperitoneally. As soon as the animal recovered his original weight a small dose 1 or 2 c.c. of a living culture was injected. In this manner, injecting the animals only when they had regained their former weight, the dose was gradually worked up to 6 c.c.

As a rule it would take the animals about two days to regain their weight after an injection of the bacilli. Two rabbits, the agglutinating power of whose serum was negative at 1 to 10 dilution were treated in the above-described manner fairly regularly from Oct. 13, 1909, to Jan. 5, 1910. On that day one was sacrificed. The serum of this animal gave a positive Widal test at a dilution of 1 to 20,000. The second rabbit was carried along in the same manner until January 24, when its serum showed a positive result at 1 to 30,000 dilution. The blood was collected for us aseptically from carotid arteries in Dr. F. P. Gay's laboratory. The blood was allowed to clot, the serum pipetted off, and cleared by centrifugalization, all under sterile conditions. The serums from the

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4. Lüdke: Deutsch. Arch. f. klin. Med., 1910, xeviii, 395.

two rabbits thus collected was kept at a temperature just above 0 C. From time to time they were injected into other rabbits with the results as shown in the accompanying tables.

The serums of the rabbits injected with the antityphoid serums were studied only in regard to their agglutinating power. In all the animals, control tests showed that normally their serum gave a negative agglutination test at a 1 to 10 dilution.

In Tables 1 and 2 the weight of the rabbit, the amount of the injection, and the strength of the agglutinating power of the injected serum are recorded; also the hour at which the animal's serum was collected and the highest dilution which gave a positive agglutination test.

TABLE 1.—RABBITS INJECTED INTRAVENOUSLY

Rabbit 1.—1540 gm. 2 c.c. 1 to 20,000 serum	Hours after injection									
	1	2	2½	3	4	5	6	7	8	24
	1:20	1:100	X	1:400	1:100	1:20	1:20	X	X	X
Rabbit 2.—1620 gm. 2 c.c. 1 to 20,000 serum	1:20	1:100	X	1:300	1:100	1:200	1:20	X	X	X
Rabbit 3.—1530 gm. 2 c.c. 1 to 30,000 serum	1:20	1:100	X	1:300	1:20	1:100	1:20	O	O	X
Rabbit 4.—1440 gm. 2 c.c. 1 to 20,000 serum	X	X	1:500	X	X	X	X	X	X	O

X in both Tables 1 and 2 means not tested.

O In both Tables 1 and 2 means Widal test negative at 1 to 20 dilution.

From a study of Table 1 it is evident that the agglutinating power reaches its height about the third hour and gradually diminishes until it disappears about the seventh hour. The height obtained is above that usually seen in the course of typhoid fever. The dose is roughly 1 c.c. to every 150 gm. of body weight.

Table 2 shows the effect of subcutaneous injection of the antityphoid serum.

From Table 2 it is evident that the height of the agglutinating power in the animals injected subcutaneously is obtained at the third and fourth hours and that it disappears at about the seventh hour. The agglutinating power does not become so powerful as after intravenous injection. J. H. Smith<sup>5</sup> in 1907 reports in his studies on the absorption of antibodies that coliagglutinins from goats, when given to rabbits subcutaneously, are slowly absorbed and reach their height only after from two

5. Smith: Jour. Hyg., 1907, vii, 205.

to three days. This is quite at variance with those results from the use of typhoid agglutinins from rabbits subcutaneously.

In order to see whether these injections, if repeated several days, would stimulate the formation of agglutinins in a rabbit, one rabbit was injected subcutaneously with 2 c.c. of the serum on the first, third, fourth and sixth days. Three days later this animal's serum showed a negative agglutination test at a 1 to 10 dilution.

TABLE 2.—RABBITS INJECTED SUBCUTANEOUSLY

Rabbit X5.—	Hours after injection—									
1480 gm. 2 c.c. 1 to 20,000 serum.....	1	2	2½	3	4	5	6	7	8	24
Rabbit 6.—1580 gm. 2 c.c. 1 to 20,000 serum	1:100	1:100	X	1:200	1:200	1:100	1:20	X	X	X
Rabbit 7.—1640 gm. 2 c.c. 1 to 30,000 serum	1:20	1:100	X	...	1:100	1:100	1:20	X	X	X
Rabbit 8.—1820 gm. 2 c.c. 1 to 30,000 serum	X	X	X	1:200	X	X	1:20	O	O	X
Rabbit 5.— Another day 1490 gm. 2 c.c. 1 to 20,000	X	X	X	1:200	X	X	1:20	1:20	O	X
	X	X	1:200	X	X	X	X	X	X	O

The facts that the agglutinating power in the injected animal only lasted a short time, and that repeated injections did not have any permanent effect, suggest that this antityphoid serum has no creative power so far as agglutinins are concerned. The agglutinins in the injected animals seem to be simply the diluted agglutinins of the serum. Let us suppose the blood to be one-fifteenth of the body weight. Rabbit 1 weighed 1,540 gm., and therefore his blood weighed 118.5 gm. Two cubic centimeters of serum were given intravenously, making a dilution of the serum after it was well mixed by the third hour of practically 1 to 60. At this hour the highest positive test was at a dilution of 1 to 400. Thus the original serum was diluted 1 to 24,000, which agrees fairly well with the 1 to 20,000 dilution at which the serum was known to give a positive test. Although the sources of error in such figuring are numerous, this result adds strength to the theory that the agglutinins in the injected animals are simply the diluted agglutinins of the antityphoid serum. In the subjects injected subcutaneously this relation does not hold so well. It is possible, however, that some of the agglutinins are lost during the absorption from the subcutaneous tissues, or that some other factor enters in.

If the agglutinins in the injected animals are simply a manifestation of a dilution of the agglutinins in the antiserum, an antiserum with a higher agglutinating power ought to produce more agglutinating power in the injected animals. To study this point, a horse serum prepared by Parke, Davis & Co. Experimental Laboratory was used. This serum gave a positive agglutination test at a dilution of 1 to 160,000. Six rabbits ranging in weight from 1,500 to 2,000 gm. were injected subcutaneously with 2 c.c. of this horse serum. Two of these gave peculiar results, being practically negative throughout. We do not know whether this was due to some error in technic or to some unrecognized factor, but we mention it in case similar results occur to others. The other four acted like the rabbits injected with rabbit serum in regard to the time at which the agglutinating power reached its height, and when it disappeared. Of these four, two showed an agglutinating power at the third hour positive at 1 to 500, one positive at 1 to 400, and one questionable at 1 to 400 dilution. Comparing this with the results obtained by injecting subcutaneously the serum weaker in agglutinins, it is evident that the more powerful the serum the greater the effect on the serum of the injected one.

Thus it seems reasonable to conclude that a serum ought to be obtainable which, when injected in amounts much less than 1 c.c. to every 750 gm., can produce a higher agglutinating power in the serum of the injected animal than occurs normally in the course of typhoid fever.

#### SUMMARY

The following is a summary of the points brought out in this work:

The agglutinating power of the serum in typhoid fever usually reaches its height in about the third or fourth week. Occasionally at this time a positive reaction will be obtained at a dilution of 1 to 600 or 1 to 800; as a rule, only at a dilution of about 1 to 250.

In rabbits, agglutinins can be developed by injecting typhoid bacilli intraperitoneally. These experimentally produced agglutinins apparently can be increased in strength as long as the bacilli are injected.

The serum from these rabbits when injected into other rabbits causes a transitory agglutinating power to appear in them. This power appears the first hour after injection, gradually increases in strength until the third hour, then subsides and has disappeared about the seventh hour. These time relations are practically the same, whether the serum is given subcutaneously or intravenously. The height of the agglutinating power is greater after intravenous than after subcutaneous injection. The

agglutinating power in the injected animals is apparently simply a dilution of the agglutinating power injected. Even repeated injections of serum fail to stimulate a rabbit to form agglutinins.

If comparisons may be drawn from animal experimentation, it should be possible in typhoid fever to administer serum in doses of practical size so as to produce more agglutinating power than ordinarily occurs in the course of the disease. In order to keep up this agglutinating power the serum should be given every few hours. The serum should preferably be given intravenously.

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# THE CUTANEOUS AND CONJUNCTIVAL TUBERCULIN TESTS IN THE DIAGNOSIS OF PULMONARY TUBERCULOSIS

## SECOND REPORT

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In May, 1909, we reported<sup>1</sup> the results of the conjunctival and cutaneous tuberculin tests in 500 patients. The present report deals with 1,000 additional patients to whom these tests were administered, and who formed the unselected material of an ambulant clinic, the Phipps Dispensary of the Johns Hopkins Hospital. We made no change in the strength of the solutions used for the eye tests, nor in the technic of the skin test, so that our last results are comparable with our earlier figures. We used one drop of a 1 per cent. solution of Koch's Old Tuberculin (human) in the left eye. In the event of no reaction we proceeded with one drop of a 5 per cent. solution in the right eye. If this, too, produced no reaction, we refrained from further instillations, fearing the possible intensity of a reaction consequent on a second instillation of tuberculin into an eye. Our fear is based on evidence, gathered accidentally, that a second instillation may give a positive and even a severe reaction in a case in which a previous similar test gave a negative result. For the skin test we make a superficial incision in the skin of the forearm through a drop of old tuberculin and, as control, through the untreated skin. In our first series we used simultaneously a 1 per cent., 5 per cent. and 20 per cent. solution for the cutaneous test, and found a comparison of the resulting reactions of no value for clinical diagnosis. We found also little difference in the reactions resulting from 20 per cent O. T. and pure O. T. We therefore limited ourselves to undiluted tuberculin, in accordance with our published conclusion that only the negative skin reaction is of value in diagnosis. For further discussion of the technic and for contra-indications to the eye test, we refer to the previous report.

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1. Hamman, L. and Wolman, S.: The Cutaneous and Conjunctival Tuberculin Tests in the Diagnosis of Pulmonary Tuberculosis. *THE ARCHIVES INT. MED.*, 1909, iii, 307.

The 1,000 cases are divided into six groups: "non-tuberculous," "doubtful," "probable," "incipient," "moderately advanced" and "far advanced." This division is based on a careful clinical study, without reference to the result of the tests. As tuberculous, we included cases with tubercle bacilli in the sputum, and those affording only the strongest clinical evidence of tuberculosis. Cases concerning which clinical observers might have even a slight doubt have been ruthlessly placed in the doubtful class, which is therefore large, in order to elicit more clearly the significance of the reactions. The probable group includes cases which most clinicians would regard as tuberculous, but for which the evidence is not absolutely convincing. The non-tuberculous group includes patients who are apparently well, or whose symptoms are demonstrably referable to some non-tuberculous cause.<sup>2</sup> The "non-tuberculous" group numbers 188; the "doubtful," 429; the "probable," 18; the "incipient," 35; the "moderately advanced," 19; the "far advanced," 191; making 305 tuberculous cases, of which 211, or 69 per cent., had tubercle bacilli in the sputum. Among the tuberculous cases of this second series, there is a greater percentage with tubercle bacilli in the sputum than in our first series, largely because we have realized more than ever the necessity of avoiding as far as possible the effect of the personal equation in adjudging a patient as having active tuberculosis. In consequence, the incipients of the second series are somewhat more advanced than those of the first; indeed are, for the most part, not strictly incipient.

Table 1 shows the result of the tests in 188 non-tuberculous cases. Note that, even in this group, a positive cutaneous reaction is frequently obtained, but note particularly that a positive conjunctival reaction to 1 per cent. O. T. occurs in only three out of 186 cases.

Table 2 gives the results in 429 doubtful cases. Here a positive skin reaction is more frequent; a positive result to the 1 per cent. eye test is still comparatively infrequent, that is, in only 15 per cent. of the cases.

Table 3 deals with the seventy-eight probable cases. A negative skin reaction is infrequent, and a negative 1 per cent. conjunctival reaction is not as predominant as in the preceding group.

Table 4 deals with the thirty-five cases in the first stage of pulmonary tuberculosis. The negative skin reactions are here scarce; a negative conjunctival reaction to the 1 per cent. solution occurs in only 31 per cent.

Table 5 presents the seventy-nine cases in the second stage. Negative cutaneous tests are rare; negative conjunctival reactions to the 1 per cent. solution occur in only 23 per cent.

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2. This group may, of course, include some individuals with latent inactive tuberculosis.

Table 6 deals with the 191 far-advanced cases. Here there is an increase in both the negative skin and eye reactions, owing to the well-known fact that the moribund, who are naturally in this group, often show no reacting power.

Table 7 shows the data of Tables 1 to 6 condensed and stated in percentages. The results shown in this table are practically the same as those in Table 7 of our first paper. The only discrepancy worth noting is in the incipient group, which shows 69 per cent. reacting to the 1 per cent eye test, against 48 per cent. of the first series. This is explained, as we have said above, by the probably more advanced condition of our incipient group in this second series, more of the real incipients being in the probable group.

The results of the 5 per cent. eye test are based on the figures given in the above tables and are estimated in the manner described in our first report. They represent what would have occurred had all of the patients received an instillation of a 5 per cent. solution in one eye. The striking feature of the skin test is the large number of positive reactions, even 57 per cent. of the non-tuberculous group. Already in the doubtful group, the number of positive reactions rises to 83 per cent. A mean between the figures of these two groups would represent about what we would expect to find in the average adult. It is clear that a positive skin reaction in an adult cannot be used as evidence of clinical tuberculosis. The next column, giving the results of the 1 per cent. eye test, is the most striking of the whole series. Only 1.6 per cent. of non-tuberculous cases give a positive reaction to this test, a result almost identical with that obtained in our first series. But note that a negative reaction to this 1 per cent. solution by no means excludes clinically active tuberculosis. The 5 per cent. eye reaction is, however, valuable in revealing some of those tuberculous cases in which there is no reaction to the 1 per cent. solution. Unfortunately in a fair number of active cases there is no reaction even to the 5 per cent. solution, and in the non-tuberculous cases a somewhat larger number of patients do react than to the 1 per cent. Still the 5 per cent. solution is of some further help, and is certainly more useful than the skin test, because it does not include nearly as many non-tuberculous individuals. By using a solution stronger than 5 per cent., we might capture the remaining tuberculous cases, but we should run the risk of obtaining too severe reactions. We have been fortunate to encounter in no case of the 1,000 anything more than a temporary inflammation of the eye, but, judging from the severity of the reaction in a few of the cases, we fear that the employment of anything



stronger than a 5 per cent. solution would produce regrettable results. For the same reason we do not care to make our initial instillation stronger than 1 per cent. We emphasize here the statement that we use a simple saline solution of Koch's Old Tuberculin, not of any precipitated tuberculin. Preparations of the latter are stronger and give different results. In brief, Table 7 shows that the positive reaction to the 1 per cent. eye test is extremely strong evidence that the case does not belong to the non-tuberculous group. A positive 5 per cent. reaction is also strong evidence in the same direction. In the skin test, a negative result alone is of clinical interest (moribund patients being of course excluded), and denotes, with a high degree of probability, either that the patient has never been infected with tubercle bacilli, or that he was infected a very long time ago. A study of the tests in those cases only in which there are bacilli in the sputum, does not show any material variation from the above figure (See Tables 8 and 9).

Table 10 is given to show the relation between the skin and eye tests. Note that in a large number of cases in which there is no reaction to the eye test there is reaction to the skin test. Evidently these two tests are not interchangeable, although they vary, roughly, in the same direction. Together they may afford more instruction than either can alone.

Table 11 is designed for a study of the prognostic value of the skin and eye tests. It has been asserted by some that a strong reacting power in a patient is auspicious, and by others that it is ominous. Our 300 tuberculous cases were classified on entrance as being in either a favorable or an unfavorable condition, the classification being based on a consideration of the pulmonary findings and the patient's general condition. Note that the negative reaction to the 1 per cent. eye test constitutes about the same percentage in each division, 27 per cent. and 31 per cent. respectively, and also that the reactions to this test form 14 per cent. in each division. Among those marked unfavorable we know of thirty-eight patients who died. In this group too the percentages are about the same. The + + + reactions seem a little more numerous, but we cannot base a conclusion on thirty-eight cases. We have regrouped these 300 cases on the basis of the stage on admission, and find that here too the percentage figures are about the same in the three classes. We cannot, therefore, attach any prognostic value to the skin and eye tests, except, of course, when in an advanced case they are negative. In a general way the tables do indicate that the tendency to react increases as the disease becomes more advanced; nevertheless, high reacting power in an individual patient does not give us any clue to his chances for recovery.

We shall here present a few figures bearing on the relation between diagnostic subcutaneous injections of tuberculin and so-called flare-ups, recurrent or secondary reactions occurring at the site of a previous conjunctival or cutaneous reaction. Out of the twenty patients who received diagnostic injections, three showed a negative reaction to all three methods, cutaneous, subcutaneous, and conjunctival. Each of these three received 10 mg. of O. T. as a maximum dose. Among the seventeen remaining cases there were eleven instances of a "flare-up" of the conjunctival reaction, eight with and three without a constitutional reaction, but in all there was a local reaction at the site of injection. Six of the eleven "flare-ups" occurred in eyes which had yielded a negative reaction to the eye test. Evidently some change occurs in the conjunctiva (or skin), even when there is no reaction, a latent change becoming manifest on the subcutaneous introduction of tuberculin, in some cases even before a constitutional reaction is elicited. On account of the occurrence of "flare-ups" in eyes which had yielded no positive reaction originally, it is more correct to use instead of "flare-up" the term "secondary reaction" as more properly descriptive; that is, a reaction secondary to subcutaneous administration.

The average interval between the instillation of tuberculin into the eye and the injection of the maximum subcutaneous dose was twenty-eight days both in the cases with and in the cases without secondary reactions. Fifty-two days was the maximum, and twelve the least interval after which a secondary reaction was obtained. Of the nine cases without secondary reactions, four received 10 mg. and one 5 mg. as the maximum dose, without constitutional reaction. The remaining four cases required on the average 4 mg. to yield a constitutional reaction, although in one instance 0.2 mg. was sufficient. In the group yielding secondary reactions, 2.6 mg. was the average maximum dose required to produce a constitutional reaction. Three of the flare-ups occurred after only 0.2 mg. One case required a maximum dose of 40 mg. to give local, constitutional, and secondary reactions, there being entirely negative results up to this dose (this patient showed profuse hemoptysis on admission to the clinic). In three of the cases with flare-ups, tuberculin had to be discontinued because of these flare-ups before a constitutional reaction appeared. Cutaneous flare-ups occur nearly always simultaneously with conjunctival flare-ups. In cases in which both eye-tests were negative, the eye receiving the 5 per cent. solution usually flared up after a smaller dose than the eye receiving the 1 per cent., and more intensely. In a few cases the dose liberating the constitutional reaction did not reawaken

a flare-up which had appeared and subsided after the smaller, preceding dose. In none of the seventeen cases can we vouch for an indisputable focal reaction. The series is too small to allow of generalization, and we present the figures simply as being of interest. There is no apparent relation between the secondary reaction and the dose of subcutaneous tuberculin, or between the secondary reaction and the prognosis.

#### GENERAL SUMMARY

The total number of cases studied in our two reports is 1,500, a number large enough to warrant cautious deductions. A comparison of the present tables with those published in 1909 shows that they are mutually confirmatory. Practically the only discrepancy is in the incipient group, and this is due to the somewhat more advanced stage of this group in the present series. For the same reason there is a smaller difference this year between the figures for the cases with and without tubercle bacilli in the sputum.

The tables show that, proceeding from the non-tuberculous group, through the doubtful and probable groups to the definitely tuberculous, there is an increasing tendency to react. In the far-advanced group there is a slight reduction, commonly recognized as due to a fall of reacting power in the moribund. These statements hold true both for the conjunctival and the cutaneous tests. There is an essential difference, however, in that in every group the number reacting to the cutaneous test is much the larger, being, even in the non-tuberculous group, so great as to invalidate the cutaneous test as a criterion of active tuberculosis. On the other hand, although a fair number of definitely tuberculous patients do not react to the eye-test (employing solutions within the limits of safety), yet only an insignificant number of the non-tuberculous group react to the 1 per cent. solution—only 1.6 per cent.

Bearing the above results in mind, we are in a position to weigh the relative importance of the cutaneous and conjunctival tests in the diagnosis of active pulmonary tuberculosis, and particularly of early tuberculosis. As the specificity of the reactions is now well established, in the sense that only patients who have at some time been infected by tubercle bacilli can react, the skin test shows that a large number of healthy people have been so infected. But, as the test remains positive even when the infection has been successfully overcome, the story it tells is of absorbing interest to the clinician only when the

patient is still in his infancy, since a reaction during the first year or two of life means that the patient has only recently been attacked, and must be strengthened for combat with the invader. But, if the test is negative, and the young patient is evidently not moribund (or in the grasp of measles), any gloomy suspicions as to the tuberculous cause of existing symptoms are fortunately dispelled.

The significance of a negative skin reaction is not absolute. There is some evidence to show that after many years a positive reaction may fade, as it were; and then there is always the possibility of a fault in technic. But the younger the patient, the more nearly absolute is the meaning of a negative skin reaction as to the absence of any active or inactive tuberculous infection.

The conjunctival test, if we employ only solutions not strong enough to threaten the safety of the eye, is not nearly so sensitive as the cutaneous test. In the event of a negative reaction, entire reliance must be placed on other methods of investigation, for the patient may indeed be either definitely tuberculous, or may soon become so. But if the test results positively, concomitant with suspicious symptoms or signs, such a result is strong presumptive evidence of the existence of an active lesion. For, of patients who were followed for a considerable period, and remained well, only 1.6 per cent. reacted to the 1 per cent. solution. We do not mean that a patient, apparently well, should be condemned to treatment solely because he reacts to the 1 per cent. eye-test; but we do believe, on the evidence here furnished, that an individual reacting to the eye-test, and especially to the 1 per cent. solution, even if the examination is otherwise negative, should remain under medical surveillance for a considerable time.

While we believe with Roepke<sup>3</sup> that the reacting power tends to increase with the stage of the disease, rather than with Wolff-Eissner, who at times intimates that the reactions predominate in the early cases, yet we do not agree with Roepke in his underestimation of the value of the eye-test in the diagnosis of early pulmonary tuberculosis. A test that includes only 1.6 per cent. of non-tuberculous individuals, but as much as 40 per cent. of probably tuberculous and 69 per cent. of first stage patients, is certainly not to be ignored, but must, on the contrary, be accepted as a valuable aid in our efforts to gather under medical supervision as many as possible of the very early cases, while excluding as

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3. Roepke: Beitr. z. Klin. d. Tuberk., 1908, xi, 245.

many as possible of inactive cases with very slight signs and with entirely unrelated, if suggestive, symptoms.

The subcutaneous test to our mind shares the weaknesses of the cutaneous test. It is too all-embracing. Nor has it been established that a patient reacting to the smaller dose has the more active lesion. Certainly the individuals reacting constitutionally to a subcutaneous injection cannot be assumed, therefore, to have been in any danger of developing active tuberculosis. True, much stress has been laid on the focal reaction occurring in the lung itself; but we find that it is extremely rare in the ordinary suspect to elicit an indisputable increase of the pulmonary signs. However it may be in patients with comparatively large lesions—and to such we fear to give the subcutaneous test—those with doubtful lesions only very rarely show a definite increase in the physical signs, in spite of our anxiety to discover them. For this reason, and moreover, because we really do not know whether in the event of a focal reaction actual harm has not been done, we think the subcutaneous test much less valuable than the eye test.

The undoubted occasional recurrence or flare-up of a cutaneous or conjunctival reaction after the administration of tuberculin subcutaneously has led some to advise against the use of the eye-test in patients who may be subsequently treated with tuberculin. We, ourselves, have treated many patients with tuberculin subcutaneously and have found this danger entirely negligible. It must be remembered that in our use of tuberculin therapeutically we try to avoid, and can avoid, constitutional reactions, and that in the absence of a constitutional reaction a flare-up is rare. If the tuberculin, however, is administered suddenly in large doses, as for diagnostic purposes, even a severe flare-up is frequently encountered. It is therefore quite inadvisable to use the subcutaneous test subsequently to the eye-test, unless, indeed, after a considerable interval. The subcutaneous test can well be dispensed with, however, as its information is of little value to those interested in the diagnosis of early pulmonary tuberculosis.

Finally we must add our conviction that a thorough physical examination, a painstaking anamnesis, and an examination of the sputum are, of course, indispensable in the study of any patient. We must repeat, too, that our results with the eye-test are based on the use of solutions of a definite strength, used in a definite and limited order.

TABLE 1.—CUTANEOUS AND CONJUNCTIVAL TUBERCULIN REACTIONS IN 188 NON-TUBERCULOUS CASES

Strength of Tuberculin Reactions:	No. Skin Reactions Pure	No. Conjunctival Reactions Instillation	
		First	Second
		1%	5%
—	80	183	121
+	92	1	8
++	12	1	1
+++	2	1	0
?	2	2	55

In this and the following tables the interrogation point (?) stands for "not given."

TABLE 2.—CUTANEOUS AND CONJUNCTIVAL TUBERCULIN REACTIONS IN 429 DOUBTFUL TUBERCULOUS CASES

Strength of Tuberculin Reactions:	No. Skin Reactions Pure	No. Conjunctival Reactions Instillation	
		First	Second
		1%	5%
—	73	365	205
+	278	38	33
++	65	16	26
+++	11	9	11
?	2	1	91

TABLE 3.—CUTANEOUS AND CONJUNCTIVAL TUBERCULIN REACTIONS IN 78 PROBABLY TUBERCULOUS CASES

Strength of Tuberculin Reactions:	No. Skin Reactions Pure	No. Conjunctival Reactions Instillation	
		First	Second
		1%	5%
—	5	45	18
+	55	11	11
++	11	15	7
+++	7	7	3
?	0	0	6

TABLE 4.—CUTANEOUS AND CONJUNCTIVAL TUBERCULIN REACTIONS IN 35 INCIP-  
IENT CASES

Strength of Tuberculin Reactions:	No. Skin Reactions Pure	No. Conjunctival Reactions Instillation	
		First	Second
		1%	5%
—	2	11	4
+	22	12	5
++	8	8	...
+++	2	4	...

TABLE 5.—CUTANEOUS AND CONJUNCTIVAL TUBERCULIN REACTIONS IN 79 MODERATELY ADVANCED CASES

Strength of Tuberculin Reactions:	No. Skin Reactions Pure	No. Conjunctival Reactions Instillation	
		First	Second
		1%	5%
—	2	18	...
+	48	26	...
++	20	19	...
+++	8	16	...

TABLE 6.—CUTANEOUS AND CONJUNCTIVAL TUBERCULIN REACTIONS IN 191 FAR-ADVANCED CASES

Strength of Tuberculin Reactions:	No. Skin Reactions Pure	No. Conjunctival Reactions Instillation	
		First	Second
		1%	5%
—	16	62	25
+	133	64	16
++	30	40	6
+++	10	23	3
?	2	2	14

TABLE 7.—TABLES 1 TO 6 CONDENSED AND STATED IN PERCENTAGES

Strength of Tuberculin Degree of Reaction	Per Cent. of Skin Reactions Pure		Per Cent. of Conjunctival Reactions			
	Pure		1%		5%	
	Neg.	Pos.	Neg.	Pos.	Neg.	Pos.
Cases:						
Non-tuberculous cases	43	57	98.4	1.6	92	8
Doubtfully tuberculous cases	17	83	85	15	64	36
Probably tuberculous cases	7	93	60	40	27	73
Incipient tuberculous	6	94	31	69	14	86
Moderately advanced tuberculous	3	97	23	77	8	92
Far-advanced tuberculous	8	92	33	67	17	83

TABLE 8.—CUTANEOUS AND CONJUNCTIVAL TUBERCULIN REACTIONS IN CASES IN WHICH TUBERCLE BACILLI APPEARED IN THE SPUTUM

*Incipient Cases, 19*

Strength of Tuberculin Reactions:	No. of Skin Reactions Pure	No. of Conjunctival Reactions	
		1%	5%
—	1	6	1
+	13	6	3
++	3	4	..
+++	1	3	..
?	1	..	..

CUTANEOUS AND CONJUNCTIVAL TESTS

Moderately Advanced Cases, 54				
	Pure	1%	5%	
—	2	16	4	
+	36	18	3	
++	12	12	2	
+++	4	8	1	
?	6	..	..	

Far-Advanced Cases, 138				
Reactions:				
—	13	40	17	
+	94	52	12	
++	20	29	5	
+++	9	15	1	
?	2	2	7	

TABLE 9.—DATA OF TABLE 8 STATED IN FORM OF PERCENTAGES

	Skin Reactions		Conjunctival Reactions			
	Pure		1%		5%	
	Neg.	Pos.	Neg.	Pos.	Neg.	Pos.
19 Incipient cases .....	6	94	31	69	8	92
54 Moderately advanced cases.....	4	96	29	71	12	88
138 Far-advanced cases .....	10	90	29	71	15	85

TABLE 10.—RELATION BETWEEN THE CUTANEOUS AND CONJUNCTIVAL REACTIONS

Conjunctival Reactions to  
First Instillation  
of 1%

Reactions:	Cases	Skin Reactions (Pure)							
		—		+		++		+++	
		No.	Pct.	No.	Pct.	No.	Pct.	No.	Pct.
—	680	166	24	418	62	80	12	16	2
+	153	8	5	118	77	24	15	3	2
++	97	3	3	60	64	25	26	9	9
+++	60	2	3	29	48	18	30	11	18

TABLE 11.—A STUDY OF THE PROGNOSTIC VALUE OF THE TESTS IN 300 TUBERCULOUS CASES

Strength of Tuberculin	Per Cent. of Skin Reactions Pure					Per Cent. of Conjunc- tival Reactions				
						1%				5%
Degree of Reaction	—	+	++	+++	—	+	++	+++	—	+
116 Favorable condition ....	5	60	28	7	27	32	27	14	11	89
118 Unfavorable condition ....	9	71	14	6	31	36	19	14	14	86



38 Died . . . . .	10	75	10	5	26	33	20	20	13	87
34 Incipient										
cases . . . . .	6	65	23	6	31	34	23	12	14	86
77 Moderately										
advanced . . . .	3	61	26	10	23	33	24	20	8	92
186 Far-										
advanced . . . .	8	70	16	6	33	34	21	12	17	83

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NOTE.—Additional references consulted in preparing this article are the following:

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# A HISTOLOGICAL STUDY OF THE SWEAT-GLANDS IN CASES OF CHRONIC NEPHRITIS \*

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## GENERAL CONSIDERATIONS

The belief that impurities might be removed from the body by means of sweating dates from ancient times. Civilized nations have shared this belief with savages. The use in all parts of the world of natural thermal baths, hot-air baths, vapor baths and wet packs testifies to a universal faith in the skin as an organ of elimination. The standard text-books on the practice of medicine, under the heading of the treatment of nephritis or uremia, recommend baths or other means of securing free perspiration. They usually imply, if they do not specifically state, that the work of the kidneys may be lightened through the excretion of solids by the sweat-glands. Some, like Von Noorden, doubt that the sweat-glands excrete a sufficient amount of solids to be of value, although agreeing that the removal of water may be beneficial.

Analyses of perspiration from healthy persons show that it contains only a small amount of solids in solution. Sodium chlorid predominates among these solids, which is of interest in connection with the theory that retention of chlorids in the tissues favors edema and with the use of sweating to relieve edema. Persons who exercise violently may, however, excrete an appreciable amount of nitrogen in the perspiration. In the experiments of Benedict, as much as 0.22 gm. nitrogen was excreted per hour (equivalent to nearly 0.5 gm. of urea<sup>1</sup>). The phenomenon of an excretion of urea by the sweat-glands to the extent of coating the skin with crystalline scales is described in text-books.

It seemed to me that the facts just stated suggested that a study of the sweat-glands in cases of chronic nephritis might be at least interesting. However, it has not been the purpose of this study to establish any relation between nephritis and such well-known diseases of the skin as eczema, which has sometimes been ascribed. No cases of obvious skin disease have been considered. A further reason for examination of the

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\* Presented at the meeting of the Association of American Physicians, May, 1910.

1. Benedict: *Am. Medicine*. 1906. xi. 105.

sweat-glands in cases of chronic nephritis has seemed to be the relation, which is quite generally admitted, between gastro-intestinal inflammations and chronic renal affections. The practice of giving saline purgatives in the hope of aiding the kidneys in nephritis seems to be universal. In explanation of these gastro-intestinal inflammations some writers hazard the assertion that the intestine may vicariously assume the function of eliminating when the work of the kidneys is insufficient, and that the intestine may suffer in the process. By analogy, it appears not impossible that the sweat-glands likewise might suffer under similar circumstances. I have made no attempt to examine the literature, but if pathological conditions of the sweat-glands in cases of nephritis have been described, it is apparently at least not a matter of general information.<sup>2</sup>

#### NORMAL HISTOLOGY

A few features in the normal histology of the sweat-glands may be briefly reviewed. The duct, of course, begins as a spiral cleft in the epidermis which receives an epithelial covering of its own, continuous with the deeper layers of the epidermis, where it enters the true skin. The duct continues, to become the coiled portion of the gland, deep in the true skin or in the adjacent subcutaneous tissue. The structure of the duct extends into the coil for a considerable distance (about one-fourth of the length of the coil). The duct is lined with two or three layers of somewhat flattened epithelial cells, whose borders next to the lumen are differentiated into a narrow, homogeneous cuticle. The duct is surrounded by a delicate basement membrane, more delicate than that of the secreting portion of the tube. In the secreting portion of the coil, the epithelial cells are cubical or columnar, one layer deep (Fig. 6). Inside of the basement membrane are a few longitudinally elongated cells, not forming a continuous layer. They are usually regarded as muscle-fibers.

The lumen of the gland or duct may contain amorphous or granular eosin-staining material, evidently precipitated or inspissated secretion. It is stated that following active secretion the cells of the secreting tube become shrunken. These last two points are important in estimating pathological conditions. According to Unna, the sweat-glands secrete an oil or fat. The form of the coiled part of the gland is beautifully shown in the reconstructions of Huber and Adamson.<sup>3</sup> The average diameter of the whole coil is a little less than 0.5 millimeter. There is an abundant plexus of blood capillaries among the tubes.

2. See the recent article by Cesario Demel: *Sull'anatomia patologica delle ghiandole sudorifere*, *Patologica*, 1908-09, i, 25.

3. Huber and Adamson: *Contributions to Medical Research*, dedicated to Victor C. Vaughan, published by George Wahr, Ann Arbor, 1903, page 365.

## TECHNIC

Specimens of skin were taken in all cases from the sole of the foot close to the plantar fold, which proved to be much the most satisfactory location. In about half of the cases, samples were also secured from the anterior surface of the abdomen. The sole of the foot was chosen because of its abundant supply of sweat-glands, its freedom from hairs and sebaceous glands, and the possibility of securing specimens without disfiguring the body. The statements made in this paper refer to skin from the sole of the foot almost entirely. A few trials were made with skin from the axilla, but the pictures secured were so confusing that this region was not used further.

A piece of kidney was taken in all cases. Alcohol fixation, paraffin imbedding and hematoxylin and eosin staining were found most satisfactory after trying various other methods. Sections were cut to a standard thickness of 10 microns or for special purposes to 6 microns.

## PATHOLOGICAL HISTOLOGY

The cases included in the present study were seventy-five in number, mostly chronic interstitial nephritis; there were a few cases of large white kidney, pyelonephritis and tuberculosis of the kidney. The cases of chronic interstitial nephritis were of every grade, from the most trifling to the most extreme. At first, normal skin was taken for comparison from amputations of the foot from accident cases. It was soon found indispensable to know the condition of the kidney, and later, skin from autopsies only was used. The weakest point in the present work is the lack of a sufficient number of normal cases for comparison. Even from young adults, killed by violence and the like, a few contracted fibrous glomeruli and other evidences of slight chronic interstitial nephritis were frequently found.

Naturally, the skin was first examined for lesions analogous to those occurring in the kidneys. They may be grouped under several headings.

1. An increased number of cells—lymphocytes, polynuclear leukocytes, or other cells—was seen only a few times but there was no reason to connect them with the nephritis. No relation of such cells to the sweat-glands could be demonstrated, with a single somewhat doubtful exception.

2. An increase of fibrous tissue or thickening of the basement membrane about the sweat-glands was found only once in the seventy-five cases. In a structure so rich in fibrous tissue as the skin, this particular lesion is most difficult to determine.

3. Desquamation of the epithelial cells was also found exceedingly difficult to determine. In about ten cases the epithelial cells of the



Fig. 1.—Arteriosclerosis affecting a vessel close to a sweat-gland.

Fig. 2.—Solid material in the duct of a sweat gland, resembling a cast in a renal tubule.

Fig. 3.—Secreting tubule of a sweat-gland, showing the lining epithelium much shrunken.

Fig. 4.—Secreting tubules of a sweat-gland with desquamated epithelium.

Fig. 5.—Secreting tubule of a sweat-gland with polyhedral epithelial cells in layers and having a small lumen.

Fig. 6.—Secreting tubule of a sweat-gland in the normal condition, for comparison.



secreting tubes were much shrunken and distorted. The alterations were certainly due in part to drying, which the exposed position of the skin makes possible; in part they were probably the result of active secretion shortly before death (Fig. 3). I have seen a similar shrinking of the epithelium in normal skin from an amputated foot. In a few cases pathological desquamation had undoubtedly occurred (Fig. 4). Some features suggested a relation between desquamation and shrinking of the epithelium from secretion. Post-mortem changes seem to take place more easily in the epithelium of the secreting tubes than in that of the ducts. With the technic employed, the finer degenerative changes in cells would not be demonstrated. Actual necrosis of the epithelial cells with loss of nuclear stain was not seen at all.

4. Cystic dilatation of the secreting tubes was seen five times. In each case only one small cyst was discovered in several sections. In one of these it was associated with probable desquamation in other tubes and atrophy. Moderate dilatation of the ducts occurred four times; it seemed to be without pathological significance.

5. Atrophy of the secreting tubes, if present at all, was exceedingly rare. What appeared to be atrophy might have been collapse of the tubes after active secretion.

6. Casts, or bodies composed of a small amount of amorphous, slightly stringy or granular material were quite often seen in the normal secreting tubes and ducts. In seventeen cases (of the seventy-five) homogeneous material was seen in the ducts or more rarely in the secreting tubes. In cross-section, such bodies could hardly be distinguished from casts in renal tubules. In longitudinal section they were never of firm consistency along a considerable length, as is the case with renal casts (Fig. 2). Usually only one such body could be found in many sections. These bodies occurred several times in association with kidney lesions of the most trifling character. As the sweat-glands are stated to secrete an oily substance, it is very doubtful that the bodies in question have at all the same significance as casts in the tubules of the kidney. Very rarely they contained cells or were composed of desquamated epithelium.

7. Recent thrombi of the large arteries or veins were noticed frequently; old calcified thrombi of small veins four times. The recent thrombi were regarded as agonal, and none of the thrombi were in the vicinity of the sweat-glands or seemed to have any relation to them. Small amorphous masses, hyaline or calcified or both, were seen twice in the connective tissue of the true skin apparently in lymph-spaces. Their significance could not be determined, but they seemed to have no relation with the sweat-glands.

8. Arteriosclerosis or hyaline degeneration of the arteries of the skin occurred in some degree sixteen times in the seventy-five cases (Fig. 1). The changes in the arteries were sometimes, though not usually, seen in the vessels supplying the sweat-glands; but on prolonged search they would probably be found near the sweat-glands in all cases that showed arteriosclerosis in the skin. No frequent association of the arterial changes with edema could be demonstrated. As the observations were made chiefly on skin from the sole of the foot it is possible that they do not represent correctly the frequency of arteriosclerosis over the skin of the body in general. In part of the cases, skin from the middle of the abdominal wall was also studied and changes in the arteries were found there much less often than in the foot. However, since the middle of the abdomen is poorly supplied with arteries it cannot be regarded as a satisfactory control to the plantar region.

Thickening, with increase in the number of the connective tissue cells, in the walls of the small veins was seen ten times in the seventy-five cases; in four instances it was associated with old thrombosis of these veins. While it sometimes occurred in cases that showed arteriosclerosis, it was also observed independently. It is likely that the changes in the veins were partly due to local conditions in the foot. I have observed similar changes in skin from the foot in normal subjects.<sup>4</sup>

9. Finally there remains to be described a condition of the sweat-glands of whose meaning I am uncertain. Text-books on histology seem to agree that the secreting portions of the coiled tubules of normal sweat-glands are lined by a single layer of cubical or columnar epithelial cells (Fig. 6). In the cases included in this study the secreting tubes frequently were lined apparently by more than a single layer of cells. The cells were so irregularly disposed that it could hardly be said that they were arranged in layers, but, roughly speaking, they appeared to be two or three layers deep (Fig. 5). The outlines of the individual cells were often difficult or impossible to distinguish. The condition occurred at scattered points and only for a short distance along a tubule, as was shown by the examination of serial sections. The whole diameter of the tubule was large but not larger than is often seen in normal cases; the lumen was small, often very small. That such tubules were secreting tubules and not ducts was proved by their large size, the distinct basement membrane, and the muscle-cells within the basement membrane. It was naturally exceedingly difficult to prove that the appearance of having several layers of cells might not have been produced by having cut across the coiled

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4. See Martin and Meakin: *Peripheral Phlebosclerosis*, *Tr. Assn. Am. Phys.*, 1905, xx, 525.



tubules obliquely. At the suggestion of Dr. Huber, I tried reconstructing a portion of some of the tubes under discussion, but found that the direction changed so continually, not in one but in several planes, that it could hardly be said that any section was a true transverse section of a tubule. Furthermore, the course of the lumen often was more tortuous than that of the tubule as a whole. I have found secreting tubules lined by epithelial cells apparently in several layers in skin from normal cases, but rarely and in a less marked degree. The impression obtained from comparison of normal cases and cases of nephritis has been that the latter do actually show increase in the number of the epithelial cells in the tubules; and that the same may possibly occur to some extent in normal cases. As stated in the first part of this paper, its weakest point is acknowledged to be the lack of an adequate number of normal cases for comparison. In a measure this lack is compensated for by skin from mild cases of nephritis. In fourteen cases of nephritis counted as mild or trifling, the epithelial cells of the secreting tubes of the sweat-glands appeared to be in more than one layer only once; the same occurred fifteen times in sixty-one cases of nephritis regarded as moderate or severe.

Assuming that the epithelial cells actually are in layers, the significance of the change could only be conjectured. There is no evidence pointing to degeneration or desquamation; although no mitoses were seen, there appeared to be an increase in the number of cells. That, of course, does not prove the existence of a functional hypertrophy of the sweat-glands. It is interesting, however, to recall that Köster and others allege that the glomeruli and tubules of the kidney may become hypertrophied in chronic nephritis. It is also possible that contraction of the longitudinally disposed muscle-fibers beneath the epithelium might shorten the tubule and throw the epithelium into layers. I must also state again that the observations have been made almost exclusively on skin from the sole of the foot. The histories of hospital cases could not be relied on to record such a symptom as hyperhidrosis if it had been present.

#### SUMMARY

The condition just described (Section 9) will evidently require a long series of investigations for its explanation, so that a tentative presentation may be admissible now. The remainder of the work may be summarized by saying that in the seventy-five cases of nephritis where skin from the sole of the foot was studied, arteriosclerosis was the only lesion that occurred in connection with the sweat-glands frequently enough to be of great importance. Although bodies resembling casts in the renal tubules were not rare in the sweat-glands, it is very doubtful that they have the

same significance as renal casts or that they are pathological. Desquamation of epithelium, an increase of cells about the tubules suggesting inflammation, and thickening of the fibrous tissue about the tubules, were uncommon changes. While two or more of the conditions above described were sometimes seen associated in a single case, no important connection between them could be demonstrated. It seemed best to limit the scope of the present paper to an enumeration of the findings, leaving any conclusions that may be drawn for a subsequent report after more extended research.

I am indebted to Dr. Charles G. Stockton for the suggestion that led me to undertake these studies.

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## LENTICULAR ZONE AND ANARTHRIA\*

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The classical ideas concerning the question of aphasia have recently become a subject for reconsideration through the efforts of Pierre Marie.<sup>1</sup> The distinguished French neurologist, after a careful and conscientious study covering a period of several years, has endeavored to replace the old views on aphasia by a new and more simple conception. His contention is that the division of aphasia into a motor and sensory is no more tenable; that there is only one aphasia, namely: sensory aphasia, to which anarthria is sometimes added. Marie, therefore, does not recognize the motor aphasia of Broca with agraphia, but considers only total aphasias.

Since this somewhat startling announcement of Marie, made in 1906, a large number of anatomo-clinical observations on aphasia have been reported by competent observers, some corroborating and others denying the above view. In spite of the large material already accumulated the views differ widely. Indeed, so far it seems that they are even irreconcilable. One class of writers, with the masterly Déjerine<sup>2</sup> at its head, refuses absolutely to accept Marie's ideas and rejects them *in toto*. The other category of very authoritative men adhere to Marie's new conception without the least criticism. The clinico-anatomical case I am reporting demonstrates clearly, I believe, that, while certain features of Marie's revised view on aphasia are not at all in conformity with pathological findings, there are nevertheless some phases which can be explained, if not totally, at least to a large degree, on the basis of his so-called lenticular zone. The anatomical and clinical conditions of the case are particularly conspicuous with regard to the most important point of Marie's contention, namely, with the question of anarthria.

### CASE REPORT

The case is as follows:

*Patient*.—O. A., a colored man, aged 38, laborer, was admitted to the Douglass Memorial Hospital, Aug. 27, 1909, with a complete right hemiplegia. The history

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\* Read at the meeting of the American Neurological Association, held in Washington, May, 2 to 4, 1910.

1. Marie, P.: *Semaine méd.*, 1906, xxvi, 241.

2. Déjerine, J.: *Presse Méd.*, 1906, xiv, 437, 453; *l'Encéphale*, 1907, ii, 400.

shows that at the age of 23 he had had a chancre. Except smallpox, he never had any other disease and always was in good health. About one year before admission he began to feel pain in his right arm. There was a continuous aching and occasionally sharp pain would appear. Four weeks before his admission the pain became more intense. While sitting one day at the table, he made an attempt to rise, but fell, having lost power on the right side. There was no loss of consciousness.

*Examination.*—On admission to the hospital, the following condition was found: The right arm was totally paralyzed; some movements were noticeable in the right leg; the mouth was drawn to the left. While talking, saliva would run out of the right corner of the mouth. The patient had therefore a total right hemiplegia. There was considerable spasticity in the arm and leg. The knee-jerks were increased on both sides, more on the right than on the left. Ankle-clonus was present only on the right. The toe phenomenon by Babinski's method was absent on the right, present on the left; by my method present only on the left side, when the calf-muscles of the right were pressed on. There was a diminution of the sense of touch and pain on the right side. The pupils were equal and normal and reacted to light and accommodation. The eyegrounds were normal. There were no palsies of the ocular muscles. The heart showed a slight dilatation of the left ventricle; the sounds at the apex were somewhat rough. The second aortic sound was markedly accentuated. The speech showed no disturbance of articulation, the words, syllables and letters were distinctly pronounced and without the least hesitation. The speech was impaired at the onset of the apoplectic seizure, but the patient recovered it in twenty-four hours. This information was obtained from a relative with whom the patient lived.

Further investigation into the mental condition and various forms of speech gave the following result. The first disturbance noticed was the recalling of names of certain (not all) objects. The following examples will demonstrate the disorder:

"What is the name of this place" (hospital) ?

In reply, the patient smiles, makes an effort to answer, but cannot find the name.

"Is it a stable?"

"No."

"Is it a kitchen?"

"No."

"Is it an apartment house?"

"No."

"Is it a hospital?"

"Yes."

"What is this man's business" (referring to the resident physician) ?

"I can't say."

"Is he a fireman?"

"No."

"Is he a waiter?"

"No."

"Is he a tailor?"

"No."

"Is he a doctor?"

"Yes."

"What is your work?"

"I can't tell."

"Do you do writing?"

"No."

"Do you cook?"

"No."

"Are you a laborer?"

"Yes."

"In what state is Philadelphia?"

No answer.

"Is it in Maryland?"

"No."

"Is it in New York?"

"No."

"Is it in Virginia?"

"No."

"Is it in New Jersey?"

"No."

"Is it in Pennsylvania?"

"Yes."

"What is this" (watch is shown) ?

No answer.

"Is it a key?"

"No."

"Is it a lock?"

"No."

"Is it a ball?"

"No."

"Is it a watch?"

"Yes."

Several other objects were then shown, such as key, knife, penholder, etc. The patient named some of them promptly, some with delay.

The patient presented a certain degree of word-blindness. The *Saturday Evening Post* and *Illustrated Weekly Magazine* were shown him and he was asked to read the heading. He read: "Sanitarium Evening Postal and Illustrated Weekly Manager." Further test for reading showed that he missed words, syllables, letters. A partial alexia was therefore present. The test for writing could not be performed, as the right hand was completely paralyzed, the patient being right-handed. This mental condition showed at times some lapses.

"How old are you?"

"I am 24." (He is 38.)

"How long have you been married?"

"Sixteen years."

"How old were you when you got married?"

"Sixteen years."

"Are you happy?"

"Well no, I am sick. I think I have the old folks. I don't owe anybody."

The patient also repeated continually that he heard the Lord's voice and saw angels and spirits.

His memory was also somewhat deficient: he could not tell from one meal to another what was given him to eat. He also made mistakes in the days of the week. In spite of these deficiencies he could give prompt and clear answers on the subject of his illness, on the functions of his sphincters, on his comfort and discomfort; he was able to converse with the nurse and resident physician on the weather and on his family.

To sum up, he presented at the time of his admission to the hospital and for two subsequent months, complete right hemiplegia, alexia, verbal amnesia. The latter two phenomena were not complete. But what is particularly important is the total absence of motor aphasia and of dysarthria.

*Course of Disease.*—For two months the patient's condition remained unaltered. One morning he was found unconscious and agitated with convulsive movement in his right arm and leg and frothing at the mouth. The attack lasted a minute, but for two subsequent hours the arm and leg remained in a state of extreme rigidity. Moreover, the least touch of the leg or arm would produce a convulsive movement. From the moment he lost consciousness, and during the following twenty-four hours of his life, he presented a conjugate deviation of the head and eyes to the right. An attempt to turn his head to the left would not correct the direction of the eyes. During the first few hours he could not voluntarily turn the head to the left, but in the last few hours he was able to make attempts to do it, but only attempts, as he was unable to hold it in the right direction longer than for a fraction of a minute. The same can be said about the eyes. In addition to this phenomenon, the patient was unable to protrude his tongue, move his lips or utter a word. Soon he presented difficulty of swallowing and on the twenty-fifth hour he expired.

*Autopsy.*—This was performed by Drs. Bailey and Diu Guid. The brain and cord were removed. The brain presents a slightly thickened dura and along the superior longitudinal fissure on both sides subdural osseous plaques are seen; the latter are strongly adherent to the dura and pia, especially on the left side. The frontal lobes are small and a longitudinal groove is observed on the right frontal lobe at the level of transition of the frontal to the orbital lobe. The entire posterior half of the left hemisphere is congested, and the superior third of the left Rolandic area is softer than that of the right hemisphere. There is nothing special at the base. A high transverse anteroposterior section of the brain shows a more congested state of the left hemisphere than of the right. The anterior two-thirds of the left internal capsule, as is seen in Figure 1, and the antero-external portion of the left optic thalamus show marked softening and destruction.

A second lower transverse anteroposterior section shows the following condition (Fig. 2): The entire left internal capsule is totally softened. The anterior portion of it presents a shriveled, folded mass. The lenticular nucleus, the external capsule and the head and tail of the caudate nucleus are completely destroyed. The very posterior portion of the capsule and a part of the inferior longitudinal bundle surrounding the posterior cornu of the lateral ventricle are also involved. The left optic thalamus is found very much paler than the right, and the part of it adjacent to the capsule is also softened. A particularly deep destruction is seen in the portion of the softened area which is in contact with the subcortical tissue of the insula, where a deep depression is seen. The softening also extends at a certain distance into the supramarginal gyrus, but the white matter of the angular gyrus is apparently intact.

#### DISCUSSION OF CASE

If we consider here the boundaries of the so-called lenticular zone as designated by Marie, namely, a square area limited anteriorly by the white substance of the third frontal convolution, posteriorly by Wernicke's area, externally by the insula, internally by the wall of the third ventricle, and if we consequently consider the fact that the lenticular zone com-

prises the external capsule, the lenticular and caudate nuclei, the anterior and posterior segments of the internal capsule, also the optic thalamus, we must conclude that in the present case the entire lenticular zone was destroyed with the exception of the inner two-thirds of the thalamus.

According to Marie the lenticular nucleus plays an enormous rôle in phonation and in coordination of movements indispensable for articulated speech. Indeed, he says that the lenticulostriated ganglia either by themselves or through their afferent and efferent pathways represent in the mechanism of language a body far more important from a motor standpoint than the cortical center of the old Broca's view. If, however, we refer to the anatomy of the lenticular and caudate nuclei and particularly to secondary degenerations, we know that no fibers from these nuclei enter into the composition of the cerebral peduncles, and if disturbances of speech occur in lesions of the lenticular nuclei, such lesions are always accompanied by lesions of the adjacent internal capsule. It is a well-known fact that an involvement of the knee and the adjacent portion of the posterior segment of the internal capsule gives disturbances of speech of a paralytic nature, namely, dysarthria. Déjerine has shown that through this portion of the internal capsule pass fibers coming from the operculum, which is the motor center for the lips, tongue and larynx. A unilateral lesion of this center produces dysarthria or anarthria, which are well known to be paralytic disturbances of phonation and articulation of words. In the classical motor aphasia, on the contrary, there is no paralysis of the organs involved in the mechanism of phonation and articulation. In the latter, not only the spoken language is altered, but also the inner language: such a patient has no spontaneity in bringing before him auditory images; the few words that he pronounces he utters correctly, although he may accentuate syllables or letters. The dysarthric, or anarthric, on the contrary, pronounces very deficiently, but his inner language is perfectly preserved.

Applying this information to the present case, we see that Marie's contention as to the function of the lenticulostriated body cannot be confirmed entirely by the pathological findings of the present case. Indeed, the destruction of the lenticular and caudate nuclei was complete, and yet the patient did not present the least indication of dysarthria. His speech, as far as the articulation is concerned, was clear and distinct. The patient did, however, present a partial word-blindness and partial verbal amnesia, all symptoms of sensory aphasia. If we assume that, in describing his area of speech, Marie meant that a lesion in any spot of the lenticular zone will produce symptoms of aphasia (sensory or motor),



Fig 1.—Upper section showing partial destruction of the lenticular zone (see text) viz.: two thirds of left internal capsule, antero-external portion of thalamus and tissue surrounding the internal capsule.



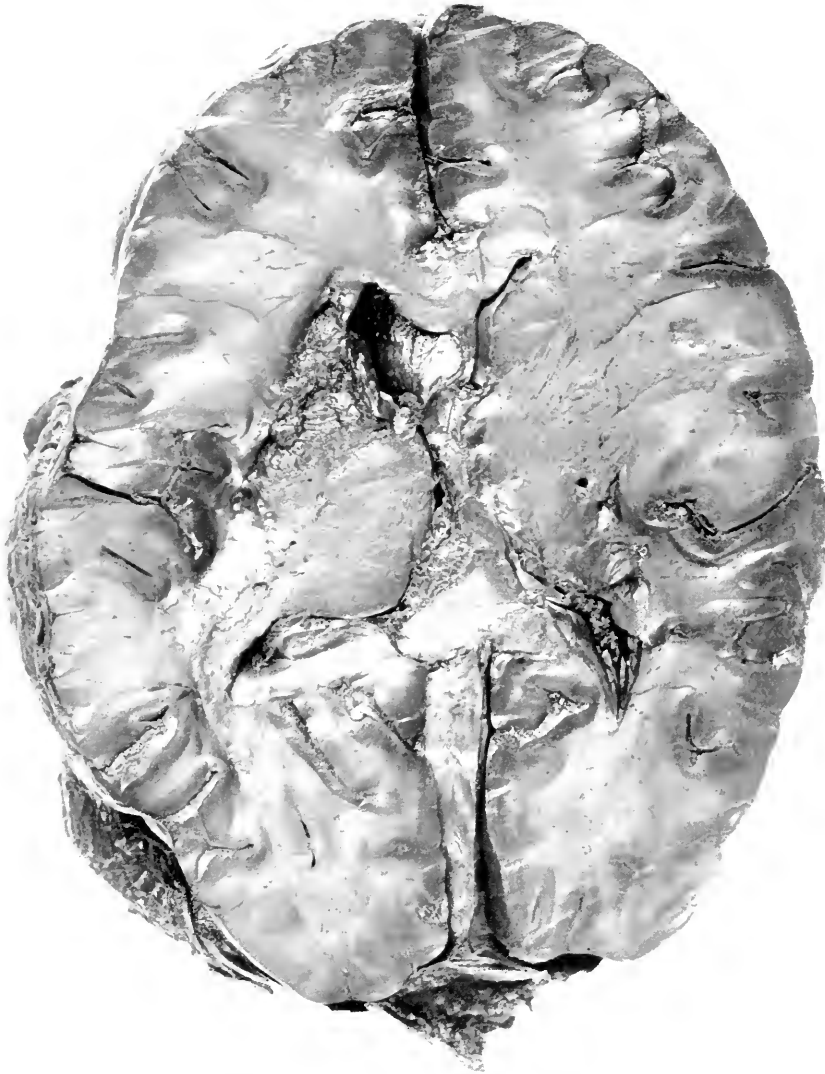


Fig. 2.—Lower section showing complete destruction of the lenticular zone (see text) viz.: entire left internal capsule, lenticular nucleus, external capsule, head and tail of caudate nucleus, part of inferior longitudinal bundle.

the present case justifies his view to some extent. The few symptoms of sensory aphasia observed in this case correspond in reality to Marie's contention, but are at variance with the old conception concerning Wernicke's zone. Indeed the angular gyrus, the supramarginal gyrus, the posterior portions of the first two temporal convolutions, the insula and the frontal convolution are all found here intact, macroscopically and microscopically. In support of Marie's conception of sensory aphasia can be mentioned also the condition of the inferior longitudinal bundle, which in my case was partly destroyed. As is well known, a lesion of this fasciculus plays, according to Marie, an important rôle in the causation of aphasia.

On the other hand, when a complete softening of the entire lenticular zone fails to produce symptoms of anarthria, on which Marie lays so much stress, and fails to present a complete picture of sensory aphasia, his doctrine does not possess so solid a basis, as one might fancy in listening to his arguments. It would, therefore, appear to be weakened by the pathological findings of the present case.

#### CONCLUSION

The conclusion to which this observation leads is that while the so-called lenticular zone of Marie may play a certain rôle in sensory aphasia, its rôle is not considerable. As to its being a center for anarthria, the present case proves that its destruction does not interfere with phonation and articulation of spoken words. Consequently, if Marie's conception of aphasia may be applicable to a certain series of cases, as he has shown, it does not hold its ground in every case in which the sensory or motor speech may become involved.

NOTE:—Since this work has been prepared, I came across Von Gehuchten's observation reported before the Académie Royale de Médecine de Belgique Jan. 29, 1910. The latter had a clinico-anatomical case almost identical with mine. There was also a vast focus of softening in the lenticular zone of the left hemisphere. It destroyed the entire external segment of the lenticular nucleus with the corresponding portion of the external capsule, the middle portion of the posterior segment of the internal capsule; it also destroyed the nucleus caudatus. The patient presented during life a right hemiplegia, but not a trace of anarthria, contrary to what might have been expected according to the views of Pierre Marie.

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## A QUICK MACROSCOPIC TYPHOID AGGLUTINATION TEST

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NEW ORLEANS

The method here proposed for making the typhoid agglutination test requires an ordinary microscope slide, or other piece of glass, a surgical needle or other puncture needle, and an ordinary medicine dropper, all costing less than 10 cents. The material required is one drop of a suspension of typhoid bacilli that should not cost more than half a cent for each test made. The time required to make the test is less than two minutes. No special bacteriological or laboratory experience is necessary; and the test, when properly performed by one with even limited experience, is as reliable and accurate as can be made by an expert bacteriologist within an hour with a microscope and the facilities of a laboratory. The test may be made at the bedside in two minutes instead of waiting hours for a report from the laboratory or a day or two as country physicians often have to do.

The material consists of a suspension of 10,000 million dead typhoid bacilli per cubic centimeter in 1.5 per cent. sodium chlorid solution to which 1 per cent. of liquor formaldehydi is added. It is stable and can be marketed as other reagents and test solutions are. Any competent bacteriologist may make up this test fluid without special facilities or knowledge required except experience in standardizing bacterial suspensions in general.

Our aim, primarily, was to develop an agglutination test practical for the general practitioner, especially those without the facilities of a laboratory and to extend the work already done by one of us (Bass) along this line. Our most sanguine expectations have been so far exceeded that we are confident that in addition to its usefulness to the country doctor and general practitioner most laboratory workers will find it advantageous to abandon the standard technic now in general use for the one here presented, provided it is given a sufficient trial.

Extravagant as the above statements and claims may appear, we make them without reservation after having made more than 100 tests comparing this reaction with the regular Widal reaction and after more than a year of experience with the test, in many cases both typhoid and non-typhoid.

The development of the test has resulted from the interpretation and application of the observation that, within certain wide limits, the more concentrated the suspension of bacteria the more rapidly agglutination takes place in the presence of a given amount of agglutinin; in addition to certain other well-known principles relative to the phenomena of agglutination. These latter we shall state or discuss only in so far as such statements or discussions may serve to explain the present test, but it will be necessary to discuss the former somewhat more at length.

#### EFFECT OF DILUTION OF SERUM ON AGGLUTINATION

Agglutination of typhoid bacilli depends on the action on the bacilli of a substance (or substances), called agglutinin, which is present in the serum, and by which they are sensitized and caused to have an affinity or



Fig. 1.—Method of holding the slide while rocking it to hasten agglutination and also proper position of slide for the reaction to be best seen.

attraction for each other. This affinity causes the bacilli to clump together when they have once come in contact with each other. Agglutinin exists in quantity quickly exhaustible under proper test, as is shown by the fact that if we add to a given quantity of the serum, containing agglutinin, an excess of bacilli and after a few minutes remove the bacilli by centrifugalization, the serum will on appropriate test be found to contain no agglutinin. If to a like quantity of the serum the same volume of salt solution be added in place of the bacillary suspension, the power of agglutination is found to be reduced only in proportion to the dilution thus brought about, and the entire volume is capable of agglutinating the same amount of bacilli as was the original serum. Therefore, within

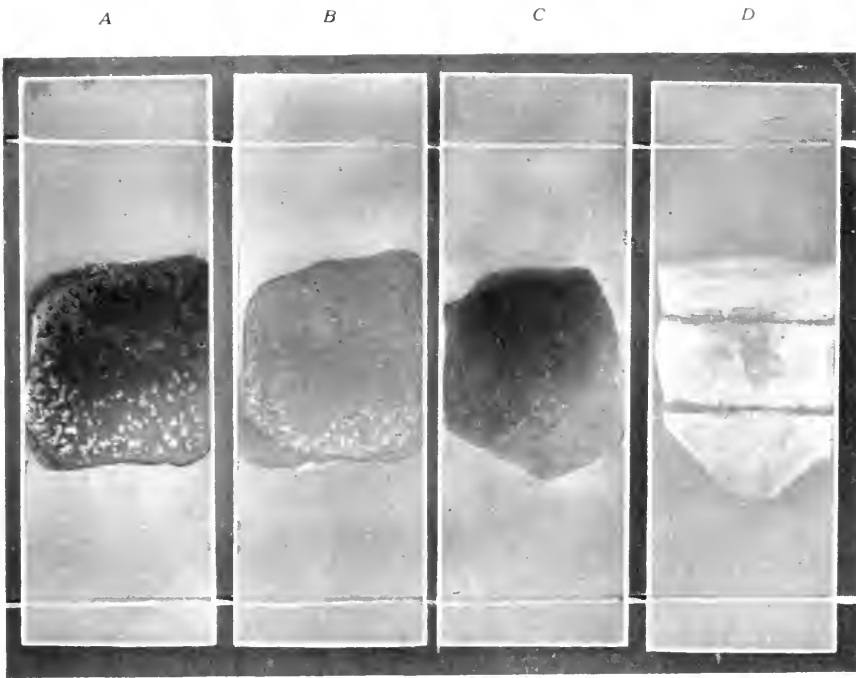


Fig. 2. Proper blood specimen and reactions in typhoid agglutination test. *A*, a good spread of blood for the test. *B*, negative. *C*, weak positive. *D*, very strong positive.



Fig. 3.—Method of holding the slide and spreading the drop of water over the spread of blood on the slide to dissolve it.

practical limits the effect of dilution of serum is relatively to reduce the agglutinin per given volume but without altering the total quantity of agglutinin.

The dilution of serum has another important influence over agglutination, viz., the more concentrated the serum the more rapidly are the bacteria sensitized. This influence is well illustrated by the following experiment. Two equal quantities of a serum are prepared by diluting one five times and the other 100 times. An amount of typhoid bacilli in suspension that has previously been found to be just capable of

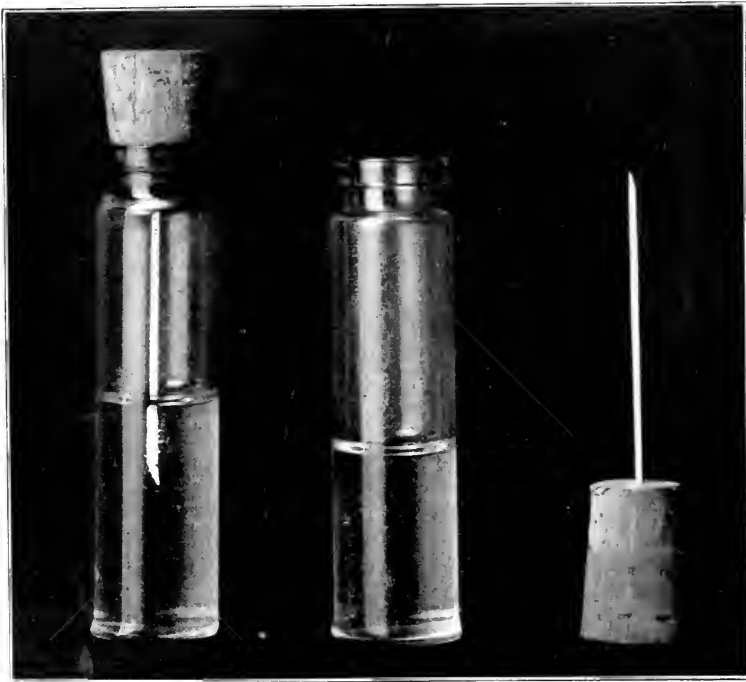


Fig. 4.—Bass' blood sticker.

exhausting the agglutinin in this quantity of serum is added to each. After one minute sufficient salt solution is added to the one-to-five dilution to bring it up to the same volume and dilution as the one-to-100 dilution. The bacilli are immediately removed with the centrifuge and the supernatant fluid is tested for agglutinin. We find that the serum which was concentrated contains little or no agglutinin, whereas the other has lost very little. On examining the bacilli from each tube we find those from the concentrated serum sensitized and agglutina-

ted whereas those from the more dilute serum are apparently not affected. If the bacilli are allowed to remain in the diluted serum an hour, and the serum and bacilli are then tested as before, we find that the agglutinin has been exhausted from each and that the bacilli are now equally sensitized and agglutinated. These experiments show that the more concentrated the serum the more rapidly sensitization occurs. The explanation for this fact lies, no doubt, in the greater distance the sensitizing molecules must travel in more dilute serums to reach the bacteria. This increases in geometric proportion with the dilution. As evidence of the correctness of this explanation we have noted that the agglutinin can be exhausted from a very weak dilution, to which bacteria have been added, in a very much shorter time by agitating the mixture or by using actively motile bacilli, a method which brings bacteria in contact or near to many more agglutinin molecules in the same length of time.

#### INFLUENCE OF DILUTION OF BACTERIAL SUSPENSION ON AGGLUTINATION

To facilitate our discussion we will take arbitrarily as a unit of bacilli 1,000,000 typhoid bacilli and, as one unit of agglutinin, that quantity necessary to agglutinate one unit of bacilli. The agglutinin content of a given serum can, for convenience, be expressed in terms of agglutinin units per cubic centimeter and may be titrated with an appropriate suspension of bacilli having a known number of units of bacilli per cubic centimeter.

On mixing bacilli suspensions of say 20,000; 15,000; 10,000; 5,000; 3,000; 2,000; 1,000; 500; and 250 units per cubic centimeter with equal quantities of a diluted serum containing 20,000; 15,000; 10,000; 5,000; 3,000; 2,000; 1,000; 500 and 250 agglutinin units per cubic centimeter respectively we found that agglutination occurred within one minute in the suspensions down to about 5,000 units per cubic centimeter but more rapidly in the stronger suspensions. We also noted that by flowing or otherwise keeping up a current in the mixture, agglutination was considerably hastened so that even the 3,000 unit specimen agglutinated in one minute. The 1,000 unit specimen agglutinates in four or five minutes if agitated or if motile bacilli are used. In the 500 unit specimen agglutination is imperfect with non-motile bacilli but if the mixture is agitated or motile bacilli are used agglutination finally occurs in ten to twenty minutes. Agglutination occurs in the 250 unit specimen in twenty to forty minutes if the same means are used but not otherwise.

If for each bacilli unit several agglutinin units are added, agglutination is hastened but only to a small extent per unit added and no amount is capable of making the 250 bacilli unit specimen agglutinate when

using non-motile bacilli without agitation. The cause of this retardation of agglutination by dilution of the bacterial suspension is, we believe, the increased distance over which many bacilli must travel (be attracted) before they get near enough to each other to clump together. In fact, our experiments indicate that in any suspension containing less than 5,000 units per cubic centimeter many of the bacteria are so far apart that the affinity or attraction they may have for each other remains inactive unless they are in some way brought closer together.

We may liken the sensitized bacteria to horseshoe magnets suspended freely by long cords. As long as the magnets are held beyond a certain distance apart the attraction they have for each other is not great enough to overcome the resistance of the air and force of gravity. Just as soon, however, as they are brought sufficiently close together their attraction for each other overcomes these influences and they jump together.

If two or three drops of an equal number of bacilli units and agglutinin units sufficiently dilute to prevent rapid agglutination are placed on two separate slides and one of them tilted from side to side in such a manner as to keep the fluid flowing while the other one remains still it is noticed that agitation very materially hastens agglutination. That this is not due altogether to the more rapid sensitization is shown by the following modification of the experiment: A suspension of thoroughly sensitized bacteria is vigorously shaken in a test-tube which breaks up the clumps to a considerable extent. Two or three drops of this are immediately placed on each of two slides and one agitated as before while the other remains still. Macroscopic agglutination is much more rapid on the slide that has been agitated, demonstrating the influence of agitation on agglutination.

#### METHODS OF MAKING AGGLUTINATION TESTS IN GENERAL USE

The Widal reaction is made very differently by different workers and the numerous methods and modifications practiced by one or another make it difficult to state just what method is most used. Few text-books give the same technic, and we seldom see exactly the same technic followed in different laboratories. The important difference lies in the time given for the reaction to occur and the kind and strength of the bacterial suspension used. Different workers require that their agglutination be complete within twenty minutes to one hour. Different workers use dilutions of serum varying from 1-40 to 1-100. The method of making the dilutions is often very inaccurate. One adds serum direct to the bacterial suspension and another dilutes it first twenty, twenty-five, forty or fifty times, and mixes equal quantities of diluted serum and culture.



There is twice as much serum used per bacilli unit in the former method as in the latter. A living twenty-four-hour-old broth culture of typhoid bacilli is generally used. Such cultures vary a great deal in their bacterial content. Some cultures contain several times as many bacilli per cubic centimeter as another of the same age and therefore require several times as much agglutinin to agglutinate them. Among the various factors that influence the strength of cultures of equal age are growth rate of the particular strain of bacilli; the number of bacilli planted; and the reaction and composition of the culture media.

Many now use a suspension of bacteria made by washing the bacilli from the surface of an agar slant culture and diluting by guess until it appears of the proper consistency. The number of bacteria here is even more indefinite as we have found by actual experiment. Another objection to the use of such bacteria for microscopic agglutination tests is that they are non-motile and non-flagellated and get together less rapidly than those from broth cultures. The same objection is made to the use of dead bacilli for microscopic agglutination tests. Dead bacilli are as susceptible of agglutination as are living bacilli, provided they are by concentration and agitation brought sufficiently close together.

#### SOURCE OF THE STANDARDS PROPOSED

In developing the present technic we have endeavored to adhere strictly to the proportions in the regular Widal reaction so far as they could be determined, and at the same time to avoid the complicating technic. That is to say, we desire to have in our final mixture the same quantity of serum per bacillus as is employed in the Widal reaction as it is generally made.

It is well known that whole blood agglutinates bacteria as well as the serum, and as it takes time and labor to separate the serum from the blood we make use of whole blood, dissolving the corpuscles out of the way with water. One part of blood dissolves in two to four parts of water but always well in four parts. We believe that blood diluted five times or one part of blood to four parts of water is about the most concentrated blood that can well be used as a routine and it is therefore the dilution we have adopted.

The average number of bacilli in a twenty-four-hour-old broth culture, such as is usually used in making the Widal reaction, has been with us about 1,000 million per cubic centimeter. If to this strength of suspension an equal amount of serum diluted fifty times be added, as is done in the most delicate Widal reaction, each bacillus will be given  $1/50,000,000,000$  part of a cubic centimeter of serum. In order to use

in the same proportion blood diluted only five times instead of fifty, it will be necessary to employ a bacterial suspension ten times as strong, or 10,000 million per cubic centimeter. This allows the same quantity,  $1/50,000,000,000$  part of a cubic centimeter of serum to each bacillus, as is employed in the average Widal reaction. We have adopted this strength and propose it as a standard until and unless future experiments should show it to be grossly at fault. We believe that there is good reason for increasing the quantity of blood per bacillus in all agglutination tests over what we estimate to be approximately the quantity allowed in the Widal reaction as generally made, but we would hesitate to change a single standard of so well-established a test unless warranted by the most extensive experimentation confirmed by many competent workers.

#### PURPOSE OF SODIUM CHLORID AND FORMALDEHYD SOLUTION IN THE BACTERIAL SUSPENSION

The dilutions of serum and bacterial suspension in making the Widal reaction are usually made with normal salt solution (0.85 per cent) and many believe this to be necessary. We question whether this has any influence on the reaction, but again in order to have our test to exactly conform to this standard test we add 1.7 per cent. salt solution to the suspension so that when equal quantities of this and the watery solution of the blood are mixed the mixture contains approximately 0.85 per cent. sodium chlorid. Adding all the salt to the one solution is of especial advantage in permitting the use of water with which to dissolve up the whole blood. Collecting whole blood is very much easier than collecting blood and separating the serum from it.

There are no doubt many germicides that would serve the purpose for which formaldehyd solution is employed in this instance but inasmuch as it seems to us to satisfy perfectly all requirements, we have adopted it without any considerable inquiry into the merits of other substances. Liquor formaldehydi kills typhoid bacilli readily in dilutions of  $1/1000$  and does not interfere with agglutination in dilutions as low as  $1/20$ . One per cent. of liquor formaldehydi is strong enough to preserve the suspension permanently and when preserved with it the bacilli retain their susceptibility to the influence of typhoid agglutinin for at least five years without any demonstrable alteration. We employ 1 per cent. of liquor formaldehydi as a preservative.

#### MAKING THE BACTERIAL SUSPENSION

If only a small quantity of the test fluid is required for individual use, it may be made by washing off the growth from the surface of a

few twenty-four- to thirty-six-hour-old ordinary agar slant cultures with 1.7 per cent. sodium chlorid solution, standardizing to 10,000 millions per cubic centimeter and adding 1 per cent. of liquor formaldehydi. The material is ready for use. It should be kept in a stoppered bottle.

If it is desired to make up large quantities, large flat culture flasks such as one quart whisky flasks or Roux's culture flasks are needed. Proper amount of ordinary nutrient agar is poured into them and after sterilization they are slanted. Agar somewhat firmer than generally employed and freshly prepared is better for this purpose than old or soft agar. An absolutely infallible and proved strain of typhoid bacilli should be selected.

Ordinary nutrient broth is inoculated and after twelve to twenty-four hours incubation, may be used to inoculate the agar slants with. Enough of the broth culture to inoculate many agar slants can be provided by inoculating several 100 or 200 c.c. Erlenmeyer flasks. Sufficient of the broth culture to cover the surface of the agar is poured into each flask, which is laid flat for a few minutes after making sure the culture has spread over the entire surface. It is an advantage to have placed the flasks in the same position for the agar to harden. The culture is incubated for twenty-four to thirty-six hours. The growth is now washed off with 1.7 per cent. sodium chlorid solution. Roux's culture flasks permit the mopping off of the culture with an absorbent cotton swab, but most of them can be washed off with the sodium chlorid solution by rocking the flasks. One quart flask will furnish from 20 to 50 c.c. of bacterial suspension stronger than 10,000 million per cubic centimeter. Care must be taken not to dilute beyond this strength. The suspension of bacilli is now drained from each flask into a funnel containing several layers of absorbent cotton and thence into a proper large bottle in which they can be kept. The entire quantity is now shaken well and a small portion removed as a sample from which to estimate the number of bacilli present per cubic centimeter.

In this work we have employed the following well-known technic: Equal quantities of the bacterial suspension and blood from the finger are mixed by means of a capillary pipette and properly spread on a slide. This is now stained and the bacteria and red cells in each of several reduced microscope fields are counted separately. It is easy to calculate the number of bacilli present per cubic centimeter if the number of red cells per cubic centimeter in the particular blood used is known. Sufficient salt solution is now added to bring the suspension to the required strength, 10,000 millions per cubic centimeter, and finally 1 per cent. of liquor formaldehydi is added. In a few minutes the material is sterile

and ready for use. The suspension should always be well shaken before it is drawn off into smaller bottles as the bacilli slowly settle to the bottom in a few weeks.

#### HOW THE TEST IS MADE

Briefly stated, the test is made as follows: Dilute the blood by dissolving it in approximately four times its volume of water. Mix one or two drops of this diluted blood on a microscope slide or other piece of glass, with an equal quantity of the test fluid. Tilt the slide from side to side or end to end (Fig. 1) so as to keep the mixture flowing back and forth. If the reaction is positive a grayish, mealy sediment appears within one minute; usually in less than that time. This consists of agglutinated bacilli and is easily seen with the unaided eye. It appears in the fluid around the edges first and tends to collect there. If the agitation is continued the clumps increase in size for two or three minutes. With blood that gives a weak reaction the appearance of the sediment is not so rapid as with stronger reacting blood. It is useless, however, to continue the test longer than two minutes, for if the reaction has not occurred in two minutes it will not occur at all. When the reaction is negative no agglutination occurs and the mixture remains as clear and unchanged as when placed on the slide.

Figure 2 *B* shows a negative reaction. Notice that the mixture is clear. Figure 2 *C* shows a mild reaction. Notice the grayish, mealy sediment. Fig. 2 *D* shows a very strong reaction with coarse sediment. Many cases of typhoid fever never give this strong a reaction. In order to make the direction as explicit as possible we call attention below to some of the minor points in the technic which are intended especially for the benefit of those not familiar with laboratory work.

#### COLLECTING BLOOD AND MAKING THE DILUTION

Though it is very desirable to be reasonably accurate in making the dilution it is not absolutely essential. At first we made the dilution by collecting one drop of blood in a bottle or small tube containing four drops of water. Recently we have improved on that, though possibly at slight sacrifice of accuracy, by spreading approximately one-fourth of a drop of blood on a slide (Fig. 2*A*) and dissolving this with one drop of water. This one-quarter drop of blood is about the quantity we use for making blood slides in examinations for malaria, differential counts, etc. When taking these an extra smear can be made, to be used for the agglutination test. Such preparations dissolve quickly. The drop of water should be spread over the blood as is shown in Figure 3 with a clean

tooth-pick, match-stick or the like. As soon as the blood has dissolved (less than one minute), one drop of the test fluid is added, the mixture agitated and the reaction noted. The specimen may be examined at the bedside or carried away and examined at some convenient time. Other specimens of blood, fluid or dry, may be diluted with approximately four times their volume of water and examined. If there are undissolved particles in the blood solution avoid these by allowing them to settle to the bottom. These or dust particles or débris from unclean slide, dropper or water may be mistaken for a positive reaction by those not familiar with the test. When one has seen a few positive reactions this could hardly occur.

In collecting blood, prick the ear-lobe or finger with a surgical needle or other such instrument, squeeze out the proper amount of blood (about  $\frac{1}{4}$  drop), touch the slide to it and spread it out with the end of another slide or other convenient thing. If no slides are at hand, collect one drop of blood in a bottle containing four drops of water. A cut of a good puncture needle or blood sticker<sup>1</sup> is reproduced here (Fig. 4). It is inexpensive, easily made and very convenient. The needle may be kept sterile by keeping a small quantity of alcohol in the bottle.

#### OCCURRENCE OF AGGLUTINATION IN TYPHOID

Typhoid cases usually do not begin to give a reaction until about the seventh to the tenth day of the disease. A few give it as early as the third or fourth day. Usually positive reactions continue throughout the disease and convalescence and sometimes a few weeks or months afterward. From 70 to 80 per cent. of all cases give a positive reaction by the end of the second week. Over 90 per cent. of all cases give a positive reaction at some time during the course of the disease but about 5 per cent. of all cases never give a positive reaction. On account of these facts, negative reactions do not eliminate typhoid from the diagnosis but their significance and value increase with the duration of the disease. Positive reactions do not occur in non-typhoid cases except those of persons who have recently had typhoid, have been vaccinated against it or are typhoid carriers. Positive reactions, therefore, are diagnostic.

Since the reaction depends on the presence of a substance, agglutinin, in the blood which develops as the disease progresses and which varies, therefore, from none at all to sometimes 100 times enough to give a positive reaction, there must be a time in every case when the quantity is not quite sufficient to cause complete agglutination and yet is enough to

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1. Described by Bass in *Medical Record*, 1910, xxviii, 538.

produce incomplete agglutination. Such instances occur to all who make agglutination tests, whatever method is followed. Fortunately these are very few and another test in a day or two usually clears up the question.

#### ADVANTAGES OF OUR TEST OVER THE USUAL METHOD

Some of the advantages of the test over the Widal reaction are:

1. It requires only two minutes, instead of an hour to make the test.
2. The test requires no laboratory experience, microscope or other laboratory facilities.
3. The physician can make his own agglutination tests reliably without depending on a laboratory.
4. The expense for each test should not exceed one-half of one cent, whereas the usual charges for agglutination tests made in the laboratories are from one to five dollars.
5. The physician can make a test every day, without sacrifice of time or money until the case is diagnosed.
6. It is not necessary to maintain a bacteriological laboratory.
7. Handling living typhoid bacilli and the accompanying risk is avoided.
8. The test is made at the bedside when the information it will furnish is most desired.

#### APPLICATION OF THE SAME PRINCIPLES IN THE DIAGNOSIS OF OTHER DISEASES AND BY OTHER WORKERS

We desire to call attention to the fact that the same principles and technic can very probably be applied to other diseases in which specific agglutinins are formed by substituting appropriate bacteria for typhoid bacilli. We have tried several different strains of typhoid bacilli and paratyphoid and find the same principles here enunciated applicable in the presence of appropriate serums. It would be practical for laboratory workers especially to test blood in this way with several strains of typhoid bacilli without much expenditure of time.

In order to ascertain the practicability of the test in the hands of the general practitioner we have sent 400 outfits for making the test (consisting of a puncture needle, medicine dropper, two dram bottle of the test suspension of bacilli, a microscope slide with some positive blood on it and directions for use) to physicians throughout the country for trial. The following reports were received up to May 1:

Typhoid cases .....	165
Reaction positive .....	140 or 92.7 per cent
Reaction negative .....	17
Reaction doubtful .....	8

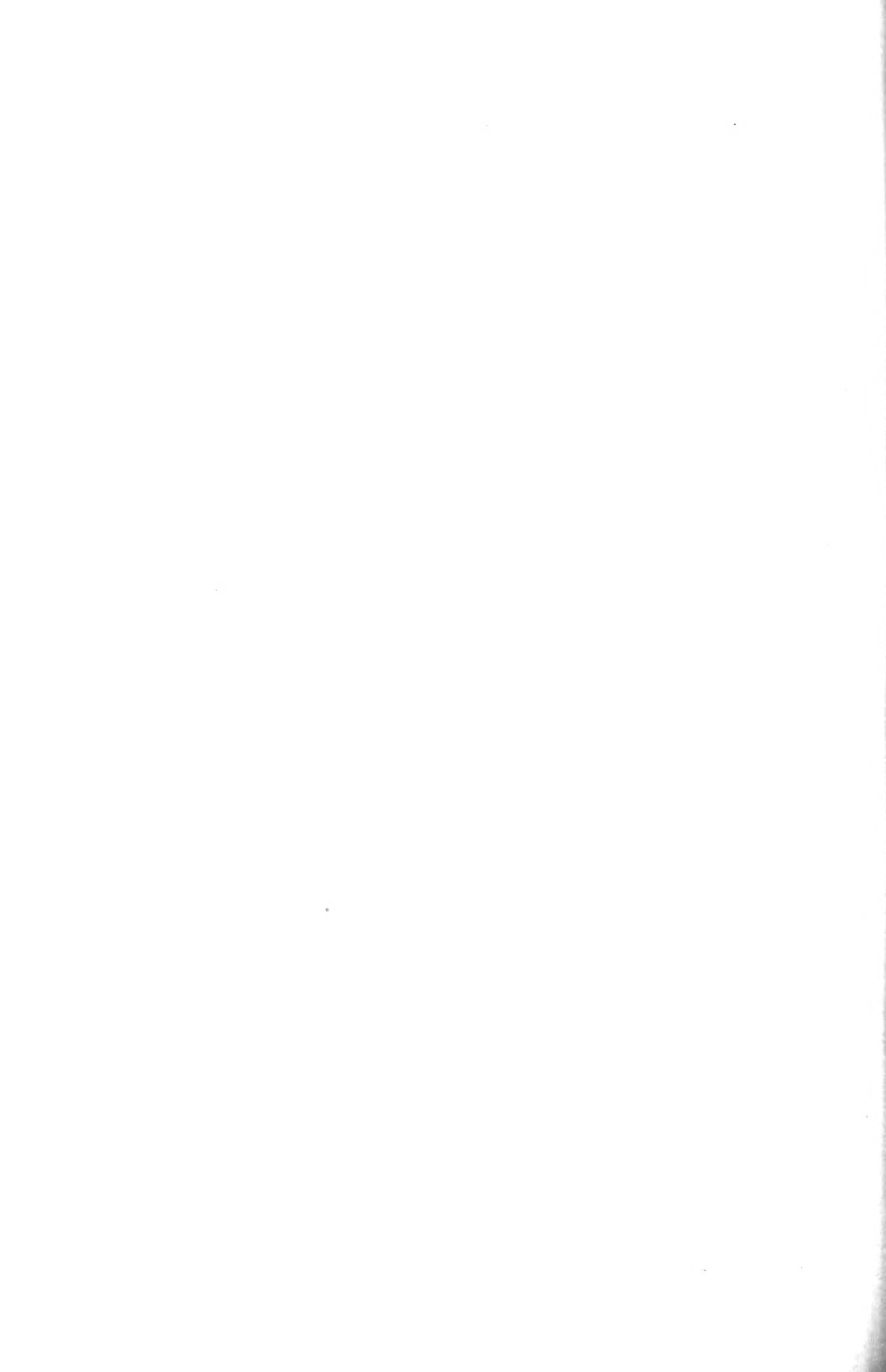
Of those reacting negatively there were three tests made during the first week.

Other conditions .....	145
Reactions positive .....	7
Reactions negative .....	138
Of those reacting positively there were—	
Continued fever .....	2
Previous history of typhoid .....	2
Lobar pneumonia .....	1
Malaria (estivo-autumnal) .....	1
Influenza .....	1

Practically all physicians heard from were able to use the test without difficulty and with perfect satisfaction.

The facilities for carrying on this work and the experiments incident thereto were furnished by the Laboratory of Clinical Medicine, Tulane University of Louisiana.

741 Carondelet Street, U. S. Marine Hospital.





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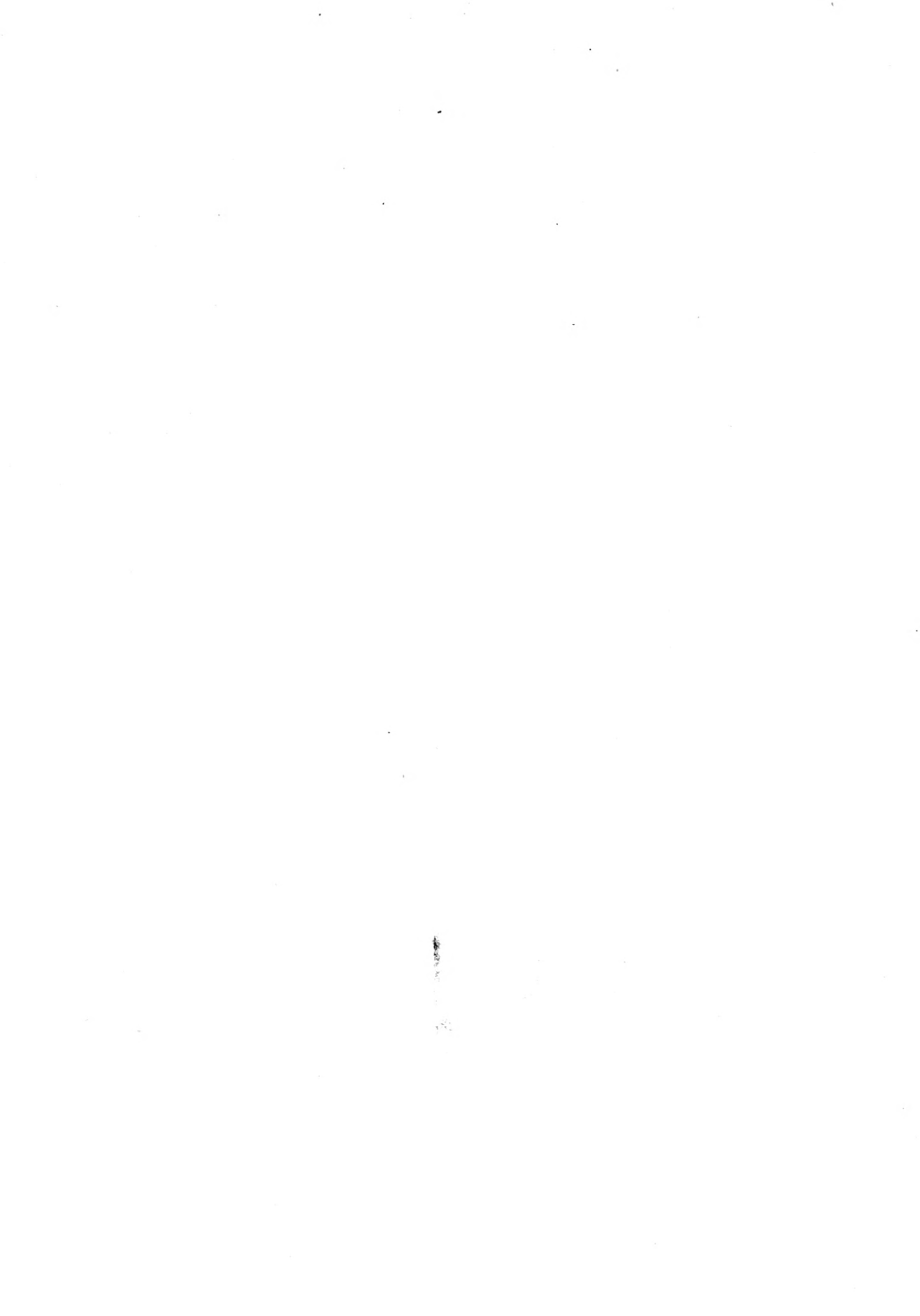
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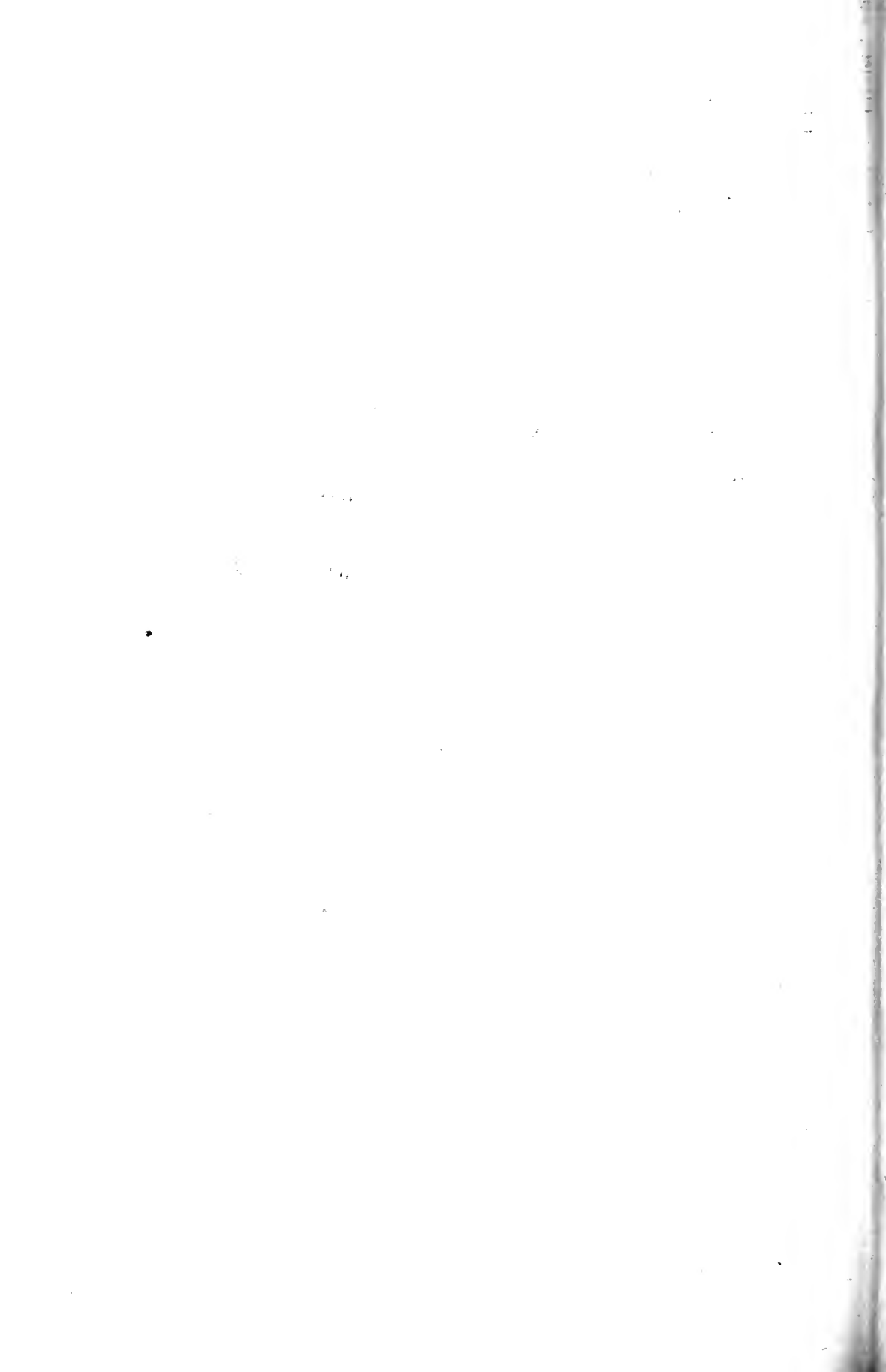
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